UNCLASSIFIED

AD NUMBER
AD234249
CLASSIFICATION CHANGES
TO: unclassified
FROM: secret
LIMITATION CHANGES
TO: Approved for public release, distribution unlimited
FROM: Distribution authorized to U.S. Gov't. agencies and their contractors; Administrative/Operational Use; 1946. Other requests shall be referred to Office of Scientific Research and Development, NRDC, Div. 9, Washington, DC.
AUTHORITY
OSRD/USAF ltr dtd 10 May 1966; OSRD/USAF ltr, dtd 10 May 1966

THIS PAGE IS UNCLASSIFIED

UNCLASSIFIED

AD 234 249

Reproduced
by the

ARMED SERVICES TECHNICAL INFORMATION AGENCY
ARLINGTON HALL STATION
ARLINGTON 12, VIRGINIA

UNCLASSIFIED

NOTICE: When government or other drawings, specifications or other data are used for any purpose other than in connection with a definitely related government procurement operation, the U. S. Government thereby incurs no responsibility, nor any obligation whatsoever; and the fact that the Government may have formulated, furnished, or in any way supplied the said drawings, specifications, or other data is not to be regarded by implication or otherwise as in any manner licensing the holder or any other person or corporation, or conveying any rights or permission to manufacture, use or sell any patented invention that may in any way be related thereto.

SUMMARY TECHNICAL REPORT OF DIVISION 9, NDRC

VOLUME 1

CHEMICAL WARFARE AGENTS, AND RELATED CHEMICAL PROBLEMS

Parts III–VI

234 249

OFFICE OF SCIENTIFIC RESEARCH AND DEVELOPMENT
VANNEVAR BUSH, DIRECTOR

NATIONAL DEFENSE RESEARCH COMMITTEE
JAMES B. CONANT, CHAIRMAN

DIVISION 9
W. R. KIRNER, CHIEF

WASHINGTON, D. C., 1946

UNCLASSIFIED

SUMMARY TECHNICAL REPORT
OF THE
NATIONAL DEFENSE RESEARCH COMMITTEE

This document contains information affecting the national defense of the United States within the meaning of the Espionage Act, 50 U. S. C., 31 and 32, as amended. Its transmission or the revelation of its contents in any manner to an unauthorized person is prohibited by law.

This volume is classified SECRET in accordance with security regulations of the War and Navy Departments because certain chapters contain material which was SECRET at the date of printing. Other chapters may have had a lower classification or none. The reader is advised to consult the War and Navy agencies listed on the reverse of this page for the current classification of any material.

CLASSIFIED TO
UNCLASSIFIED
CONFIDENTIAL

Manuscript and illustrations for this volume were prepared for publication by the Summary Reports Group of the Columbia University Division of War Research under contract OEMsr-1131 with the Office of Scientific Research and Development. This volume was printed and bound by the Columbia University Press.

Distribution of the Summary Technical Report of NDRC has been made by the War and Navy Departments. Inquiries concerning the availability and distribution of the Summary Technical Report volumes and microfilmed and other reference material should be addressed to the War Department Library, Room 1A–522, The Pentagon, Washington 25, D. C., or to the Office of Naval Research, Navy Department, Attention: Reports and Documents Section, Washington 25, D. C.

Copy No.

111

This volume, like the seventy others of the Summary Technical Report of NDRC, has been written, edited, and printed under great pressure. Inevitably there are errors which have slipped past Division readers and proofreaders. There may be errors of fact not known at time of printing. The author has not been able to follow through his writing to the final page proof.

Please report errors to:

JOINT RESEARCH AND DEVELOPMENT BOARD
PROGRAMS DIVISION (STR ERRATA)
WASHINGTON 25, D. C.

A master errata sheet will be compiled from these reports and sent to recipients of the volume. Your help will make this book more useful to other readers and will be of great value in preparing any revisions.

CLASSIFICATION CHANGED TO
CONFIDENTIAL
AUTHORITY

CONTENTS *

CHAPTER PAGE

PART III
PHYSIOLOGICAL MECHANISMS OF ACTION OF THE SULFUR AND NITROGEN MUSTARDS

19 Chemical Reactions of Sulfur and Nitrogen Mustards . . 389
20 Kinetics of Reactions of Sulfur and Nitrogen Mustards . 415
21 Effects of Sulfur and Nitrogen Mustards on Proteins, Enzymes, and Cells 431
22 Systemic Pharmacology and Pathology of Sulfur and Nitrogen Mustards 440
23 Mechanisms in Production of Cutaneous Injuries by Sulfur and Nitrogen Mustards 479

PART IV
PROTECTION AGAINST CHEMICAL WARFARE AGENTS

24 Chloramides for Protection Against Vesicants . . . 521
25 Protective Ointments 525
26 Chloramide-Impregnated Type of Protective Clothing . 529
27 Preparation of Carbon-Treated Fabrics 536
28 Deterioration, Laundering, and Decontamination Carbon-Treated Fabrics 549
29 Laboratory Evaluation of Probable Protective Value of Fabrics 553
30 Evaluation of Chloramide- and Carbon-Treated Fabrics by Means of Gas Chamber Tests and Field Wearing Trials . 557
31 Antidotes for Poisoning by Arsenicals and Other Chemical Warfare Agents 570
32 Decontamination 572

* For facility of handling, this Summary Technical Report of Division 9, Volume 1, has been bound and published in two sections. Part I and Part II will be found in the first section, pages 1-386.

CHAPTER PAGE

PART V
DETECTION AND ANALYSIS OF CHEMICAL WARFARE AGENTS

33 Introduction to Studies on Detection, Identification, Assessment, and Field Analysis of Chemical Warfare Agents 579
34 Detection of Certain Chemical Warfare Agents 581
35 Identification of Chemical Warfare Agents 588
36 Field Sampling of Persistent Chemical Warfare Agents under Subtropical and Tropical Conditions 594
37 Quantitative Determination of Certain Chemical Warfare Agents 602
38 Instrumental Methods for Determination of Certain Chemical Warfare Agents 608
39 Miscellaneous Analytical Studies 620

PART VI
MISCELLANEOUS INVESTIGATIONS

40 Synthesis of Compounds for Studies of Lubricants and Hydraulic Fluids 629
41 Special Fuels for Propulsion 634
42 Insect and Rodent Control 641
43 Synthesis of Antimalarial Intermediates and Drugs . . 651
Glossary 653
Bibliography 657
OSRD Appointees 777
Contract Numbers 778
Project Numbers 786
Index 787

PART III

PHYSIOLOGICAL MECHANISMS OF ACTION OF THE SULFUR AND NITROGEN MUSTARDS

Chapter 19

CHEMICAL REACTIONS OF SULFUR AND NITROGEN MUSTARDS

By *William H. Stein* [a]

19.1 INTRODUCTION

THE PHYSIOLOGICAL EFFECTS of a chemical agent are a consequence of chemical reactions in which the agent participates in the body. A knowledge of the nature of these reactions, therefore, should be of assistance in elucidating the physiological mechanism of the action of the war gases. In the case of the sulfur and nitrogen mustards, the work on physiological mechanism was undertaken primarily in the hope that the information thus gained would be of assistance in the design of measures to protect personnel exposed to vesicants, and would also be of aid in the formulation of a rational therapy for vesicant casualties.

In more concrete terms, it was hoped that a substance might be found which possessed the desirable properties as an antisulfur or antinitrogen mustard which have been demonstrated for 2,3-dimercaptopropanol (BAL) as an antiarsenical (see Chapter 7). The biochemical approach which led to the discovery of BAL in England prior to the entry of the United States into World War II has, therefore, greatly influenced the work on the sulfur and nitrogen mustards. It may be stated at the outset, however, that this approach has not met with success. No antisulfur or antinitrogen mustard, in the sense that BAL is an antiarsenical, has been found. Moreover, on the basis of present knowledge, it appears unlikely that one will be found. Before it became possible to draw this essentially negative conclusion, however, much work on all aspects of physiological mechanism was required.

The investigations to be summarized in this chapter have demonstrated that the sulfur and nitrogen mustards are potent and relatively nonspecific alkylating agents. In aqueous solutions, under physiological conditions of *p*H and temperature, they are capable of reacting with a vast number of functional groups residing in a host of compounds whose integrity is vital to the economy of the living cell. Among the groups with which the vesicants may react are sulfhydryl groups, carboxyl groups, primary, secondary, and tertiary aliphatic amino groups, heterocyclic nitrogen atoms (as in imidazole, proline, or pyridine), sulfide groups, and organic and inorganic phosphate compounds. The derivatives thus formed are, in almost every case, exceedingly stable compounds. Hence, under conditions compatible with cell life there appears to be little chance to effect removal of the foreign residue thus introduced. This situation is very different from that found to hold for the arsenicals.

Before an attempt can be made to elucidate the complex reactions undergone by the vesicants *in vivo*, it is necessary to have information on the general chemical reactions undergone by these substances in simpler *in vitro* systems. This chapter, therefore, will be concerned exclusively with a description of these general chemical reactions, with particular emphasis on reactions involving compounds of biological interest. Since water is an important constituent of biological systems, much attention will be directed to the transformations undergone by the sulfur and nitrogen mustards in water. In addition, it is generally believed that many of the effects of vesicants are a consequence of the reactions of these agents with tissue enzymes and proteins. This phase of the subject will be treated in Chapters 21 and 23. However, the reactions of the vesicants with amino acids and peptides, which should cast much light on the more complex reactions with proteins, will be examined in some detail in this chapter.

19.2 CHEMICAL REACTIONS OF NITROGEN MUSTARDS

19.2.1 Transformations in Water

The transformations undergone by methyl-*bis*-(β-chloroethyl)amine (HN2) in aqueous solution are given in Figure 1. The sequence of reactions given in the scheme is supported by three types of experimental evidence, namely, (1) kinetic studies in dilute solutions (up to about 0.01*M*),[1,6,10] (2) analytical studies of the reactions undergone by HN2 in aqueous bicarbonate solution (*p*H 8) and in unbuffered aqueous solution,[5,11a,13,27a,b,30,32,35,36,39,43,44] and (3) iso-

[a] Of the Rockefeller Institute for Medical Research, New York.

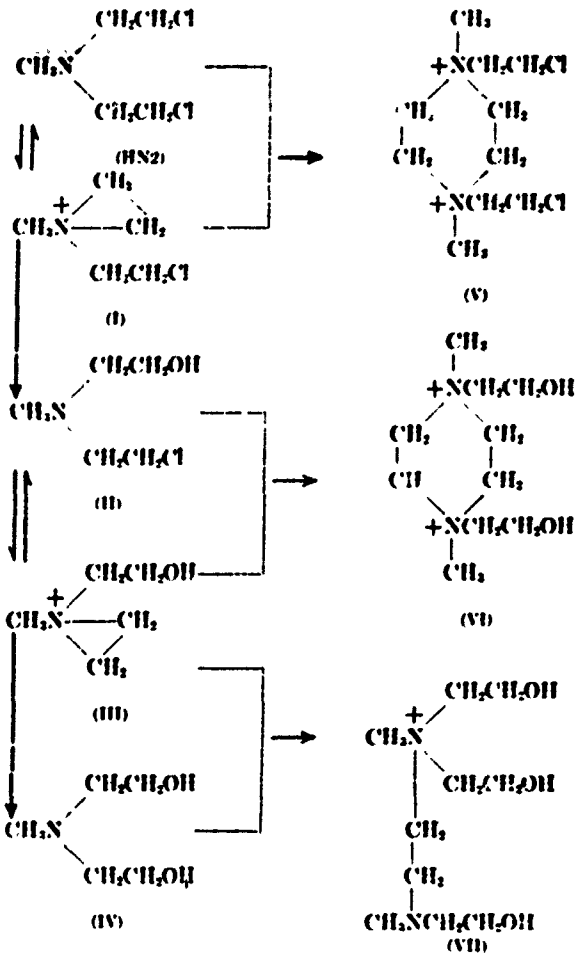


FIGURE 1. Transformations of methyl-*bis*(β-chloroethyl)-amine (HN2) in water.

lation in crystalline form of the successive transformation products of HN2 and a study of their properties.[3,5,11a,13,20,23–25,36,43] The kinetic studies are detailed in Chapter 20, whereas the other evidence is presented below.

When HN2 reacts with water at *p*H 8 (bicarbonate buffer) it goes into solution rapidly with the liberation of nearly 1 equiv of Cl^- and the appearance of negligibly small amounts of H^+ (Table 1).[5] It will be noted from Figure 1[5,22,43] that this is the result to be expected on formation of the 1-methyl-1-(β-chloroethyl)ethylenimonium ion (I). The cyclization of HN2 is a special case of the conversion of chloroalkylamines into heterocyclic compounds.[57] Additional evidence for the rapid and nearly quantitative conversion of HN2 to the ethylenimonium form is provided by the data given in Table 1 on the thiosulfate consumption of the solution. The rapid reaction of the ethylenimonium forms of HN2 with thiosulfate and the use of the thiosulfate titer as an index of ethylenimonium formation is discussed below. Conclusive evidence for the formation of I is furnished by its isolation as a crystalline salt of pierylsulfonic acid from solutions of HN2 aged for 30 minutes at *p*H 8.[5] The pierylsulfonate was identified by its elementary composition and thiosulfate titer.

TABLE 1. Hydrolysis of methyl-*bis*(β-chloroethyl)amine (HN2) in bicarbonate solution.[5]

Concentration of reactants per milliliter: 0.02 mM of HN2·HCl, 0.02 mM of NaOH, 0.08 mM of $NaHCO_3$. Temperature, 25 C; *p*H 8.

Time min	Cl^- liberated per mM of HN2 mequiv	H^+ liberated per mM of HN2 mequiv	$(Cl^- - H^+)$ mequiv	$Na_2S_2O_3$ consumed in 10 min per mM of HN2 mequiv
20	0.945	0.085	0.86	1.13
60	1.20	0.14	1.06	1.08
120	1.31	0.25	1.06	1.06
240	1.50	0.48	1.02	0.94
420	1.65	0.65	1.00	0.82
1,200	1.83	0.99	0.84	0.28
4,320	1.90	...	...	0.06*

* This value represents the thiosulfate consumed in 1 hour.

As hydrolysis in bicarbonate proceeds, there is observed a slow liberation of additional H^+ and Cl^-. The liberation of greater amounts of Cl^- than of H^+ is evidence for the formation of compounds containing quaternary nitrogen atoms. The difference between the values for Cl^- and H^+ liberated represents the amount of quaternary nitrogen present. It will be noted from Table 1 that the thiosulfate titer has decreased markedly after 20 hours without an equivalent diminution in the amount of quaternary nitrogen. This finding indicates that a portion of the intermediates having ethylenimonium rings and chloroethyl groups have been converted into quaternary nitrogen compounds which do not react with thiosulfate under these conditions.

At the end of 3 days nearly the theoretical amount of Cl^- had been liberated, and the 1-hour thiosulfate titer was very low. From such an aged solution the products isolated as pierylsulfonates were methyldiethanolamine (IV) in the amount of 55 per cent and the dihydroxy cyclic compound, N,N'-dimethyl-N,N'-*bis*(β-hydroxyethyl)piperazinium salt, in the amount of 24 per cent.[5] The dichlorocyclic dimer, N,N'-dimethyl-N,N'-*bis*(β-chloroethyl)piperazinium salt (V), is not formed in appreciable amounts in the

presence of bicarbonate, but, as will be shown later, is a major product of the reaction of HN2 in unbuffered solution. The two piperazinium derivatives V and VI, have also been synthesized.[23]

The use of thiosulfate as a reagent for ethylenimonium compounds was suggested by observations[5a] on the reactivity of solutions of HN2 with thiosulfate. The kinetics of the reaction have been studied,[10] and the product (Bunte salt) isolated.[5] It will be noted from Table 1 that the quaternary nitrogen content of the solution ($Cl^- - H^+$) does not change greatly during the transformations of HN2. This quaternary nitrogen may be either in the form of the imonium ions I and III, or the compounds V, VI, or VII. A study of the isolated products has revealed that these two types of compounds can be distinguished by their reactivities toward thiosulfate. Thus, I and III react very rapidly with thiosulfate, consuming 1 equiv within 10 minutes.[5] In the case of I, the reaction proceeds further, the remaining β-chloroethyl group cyclizes, and a second equivalent of thiosulfate is consumed within the succeeding 110 minutes. Compounds V, VI, and VII do not consume thiosulfate within 24 hours at 25 C.[5] The chlorohydrin (II) also reacts with thiosulfate,[4] presumably with prior cyclization to III, 0.66 equiv being consumed in 10 minutes. Consequently, the 10-minute thiosulfate titer of an aged solution of HN2 would measure part of the chlorohydrin in addition to the imonium ions present. In aged bicarbonate solutions of HN2, the amount of chlorohydrin present at a given time must be small, however, and the 10-minute thiosulfate titer will give a sufficiently accurate measure of the imonium ion concentration. As will be shown later, the same situation is not met in aged *unbuffered* solutions of HN2.

Additional evidence for the validity of the scheme given in Figure 1 was provided by a study of the properties of the various compounds given in the scheme, all of which have been isolated. Thus, the imonium ion (I), the isolation of which was mentioned above, when subjected to hydrolysis in aqueous bicarbonate gave analytical figures (Table 2);[5] compatible with the mechanism (Figure 1). The products of the hydrolysis of I were isolated as picrylsulfonates and found to be the linear compound (VII), and the cyclic compound (VI).[5] It will be noted in Figure 1 that the cyclization of HN2 to form the imonium ion (I) is written as a reversible reaction.[4,22,13] Evidence for the validity of this concept is provided by the kinetic studies reported in Chapter 20, and by experiments with the isolated picrylsulfonate of I. It has been found that, after treatment of the latter with dilute HCl for 20 hours at 25 C, HN2 picrylsulfonate is formed and can be isolated from the reaction mixture.[5]

The chlorohydrin, methyl-β-chloroethyl-β-hydroxyethylamine (II), has been isolated from aged unbuffered solutions of HN2 as a salt of picrylsulfonic acid.[4,5] The chlorohydrin has also been synthesized.[16,19] On hydrolysis in aqueous bicarbonate solution the analytical data (Table 2) indicate that II is transformed according to the reaction sequences given in Figure 1. From the hydrolysate the 1-methyl-1-(β-hydroxyethyl)ethylenimonium ion (III), and the cyclic compound (VI) have been isolated as picrylsulfonates.[5]

The hydrolysis of the picrylsulfonate of III was

TABLE 2. Hydrolysis of transformation products of methyl-*bis*(β-chloroethyl)amine (HN2) in bicarbonate solution.[5]

Concentration of reactants per milliliter: 0.02 mM of picrylsulfonate of I, II, or III; 0.08 mM of $NaHCO_3$. Temperature 25 C; *p*H 8 (unless otherwise noted).

Time min	Cl^- liberated per mM		H^+ liberated per mM			$Na_2S_2O_3$ consumed in 10 min per mM		
	I	II	I	II*	III	I	II	III†
	mequiv	mequiv	mequiv	mequiv	mequiv	mequiv	mequiv	mequiv
20	0.09	0.62	0.30	0.01	..	1.07	0.89	...
60	0.27	0.89	0.44	0.03	0.12	0.92	0.90	0.84
120	0.59	...	0.78	...	...	0.84	...	...
180	...	0.90	...	0.14	0.26	...	0.85	0.69
240	0.89	...	1.19	...	...	0.54	...	...
420	0.94	...	1.37	...	...	0.29	...	...
1,200	0.97	1.02	1.68	0.46	0.67	0.00	0.36	0.03
2,400		1.03		0.69		...	0.00	..

* Corrected for H^+ arising from picrylsulfonic acid. This was found to be 1 mequiv per mM of II picrylsulfonate.

† The rate of decomposition of III in this experiment appears to be more rapid than in the case of the aging of the chlorohydrin (II). In the latter experiment the initial *p*H was 7.3 and rose to 8.2 after 20 hours, whereas in the experiment with III the initial *p*H was 8.4 and rose to 8.7 after 20 hours. The lower initial *p*H in the chlorohydrin experiment may, therefore, explain the greater persistence of III in the aged chlorohydrin solution.

also studied (Table 2). The data indicated that III was transformed into VII and methyldiethanolamine in 20 hours. Both substances were isolated from the hydrolysate as pierylsulfonates, the amount of VII corresponding to 63 per cent of the theoretical maximum. Compound VI was not obtained.[4]

It should be pointed out that, after hydrolysis of HN2, the relative amounts of the various end products given in Figure 1 will vary depending upon the concentration of HN2 employed. In very dilute solutions hydrolysis to methyldiethanolamine predominates (Chapter 20). As the concentration of HN2 is raised, however, formation of compounds such as V, VI, or VII is increased, and hydrolysis is reduced.

The possible use of the nitrogen mustards as water contaminants made it imperative to study in some detail the reactions of these compounds in unbuffered aqueous solution.[4,11a,13,27a,b,32,35,36,42,43] Particularly was this the case since it had been found that, upon standing at room temperature for 48 hours or longer, 1 per cent aqueous solutions of HN2 exhibited a neurotoxic action upon administration to experimental animals.[27a,b,32,35,36]

The aging of 1 per cent aqueous solutions of HN2 was followed by determination of H^+ and Cl^- liberation and thiosulfate titers. The solutions reached a steady state in from 48–72 hours, and the toxicity remained unaltered over a period of weeks.[27a,b,32,35,36] The composition of 1 per cent solutions of HN2 aged for 48 hours was studied, and it was found, by fractionation of picrates,[32] that the solutions contained 25 per cent of the dimer (V), 15 per cent of unchanged HN2, and 35 per cent of the chlorohydrin (II). Later these figures were amended to 25 per cent of V, 20 per cent of unchanged HN2, 35 per cent of the chlorohydrin (II), and 20 per cent of methyldiethanolamine.[36,42] The values for the last two compounds were based on analytical rather than isolation data. It was found, however, that pierylsulfonic acid was a better reagent than picric acid for the isolation of the components of aged solutions of HN2; cleaner separations and much higher total yields were obtained. Accordingly, the pierylsulfonate isolation procedure was applied to the following 48-hour aged solutions of HN2:[4,13] (1) a 1 per cent solution of the free base, (2) a 1 per cent solution of the base containing 1 equiv of NaCl (from neutralization of HN2·HCl), and (3), a 1.56 per cent (0.10 *M*) solution of the base containing 1 equiv of NaCl. The results of these experiments are given in Table 3.[13] It will be noted that the presence of NaCl and or an increase in initial concentrations of HN2 leads to an increase in the amount of the dimer V, and a decrease in the extent of hydrolysis. The amount of unchanged HN2 remains fairly constant.

Prior to the isolation procedure, the aged solutions were analyzed for Cl^- and H^+ liberated, and 2-hour thiosulfate titer. A comparison of the analytical and isolation data (Table 4)[13] should reveal changes in the composition of the aged solutions produced by the experimental procedures incident to the isolations. The data in Table 4 indicate that all of the carbon-bound chlorine has been accounted for, but that there remains unaccounted for some quaternary nitrogen containing material which reacts with thiosulfate. This material is probably the imonium ion (III). Some methyldiethanolamine also has probably escaped isolation.

From the results given above, it would appear that the composition of 48-hour aged solutions of HN2 is known within narrow limits. The toxicity of such solutions may be ascribed to the presence of the chlorohydrin (II), unchanged HN2, and possibly also to a small amount of the imonium ion (III).[5,11a,13,27a] For the decontamination of water supplies, therefore, procedures should be directed to the removal or destruction of these substances.

Studies similar to those given in detail for HN2 have also been performed on several other members of the nitrogen mustard series (for kinetic studies see Chapter 20). They may be summarized briefly as follows: In the case of ethyl-*bis*(β-chloroethyl)amine (HN1), the same series of reactions given in Figure 1 have been found to occur.[5,11a,43,44a] It is noteworthy,

TABLE 3. Composition of 48-hour aged solutions of methyl-*bis*(β-chloroethyl)amine (HN2).[13]

Concentration of HN2, per cent	NaCl	Components isolated: Dichlorocyclic dimer (V), per cent	Chlorohydrin (II), per cent	Methyldiethanolamine (IV), per cent	Unchanged HN2, per cent	Total per cent
1	Absent	22	58	2	11	93
1	Present	31	49	3	9	92
1.56	Present	44	39	0.3	8	91.3

TABLE 4. Analysis of 48-hour aged solutions of methyl-*bis*(β-chloroethyl)amine (HN2).[42] (Values in parentheses are calculated from isolation data given in Table 3.)

Concentration of HN2, per cent	NaCl	Cl^- liberated per mM HN2 mequiv	Carbon-bound Cl per mM HN2 mequiv	H^+ liberated per mM HN2 mequiv	Quaternary N ($Cl^- - H^+$) mequiv	$Na_2S_2O_3$, consumed in 2 hrs per mM HN2 mequiv
1	Absent	1.00 (0.84)	1.00 (0.91)	0.66 (0.62)	0.34 (0.22)	0.87 (0.80)
1	Present	0.99 (0.86)	1.01 (0.98)	0.64 (0.55)	0.35 (0.31)	0.73 (0.07)
1.56	Present	1.00 (0.84)	1.00 (0.99)	0.54 (0.40)	0.46 (0.44)	0.03 (0.55)

however, that HN1 appears to form dimeric products, analogous to V or VI, much less readily than does HN2.[5,11a,42] The following transformation products have been isolated from aged solutions of HN1, and their chemical and toxicological properties investigated (see Chapter 22): 1-ethyl-1-(β-chloroethyl)ethylenimonium picrylsulfonate,[5] ethyl-β-chloroethyl-β-hydroxyethylamine picrylsulfonate,[5] 1-ethyl-1-(β-hydroxyethyl)ethylenimonium picrylsulfonate.[5] The dimeric compound, N,N'-diethyl-N,N'-*bis*(β-chloroethyl)piperazinium dichloride, has not been obtained after hydrolysis of HN1 in water, but has been isolated from aged methanolic solutions of HN1.[42] Formation of the dimer is noticeably slower in the case of HN1 than in the case of HN2.[42]

The reactions in water of other homologs of HN2 have also been studied, although not in so great detail (see Chapter 20). The behavior of the *n*-propyl and isopropyl compounds has been found to resemble HN1 rather than HN2.[42] Thus, both compounds show little if any tendency to form dimeric products. N,N'-di-*n*-propyl-N,N'-*bis*(β-chloroethyl)piperazinium dichloride has been isolated from aged methanolic solutions of *n*-propyl-*bis*(β-chloroethyl)amine, but the corresponding isopropyl compound could not be induced to dimerize under these conditions.[42]

The transformations undergone by *tris*(β-chloroethyl)amine (HN3) in water have been studied in detail.[5,11a,27b,c,42] This substance differs from HN2 and its homologs in that it possesses a markedly lower solubility in water. Qualitatively, however, HN3 behaves in a manner analogous to HN1, with the exception that three imonium ions are formed successively from the three β-chloroethyl groups. The first imonium form, 1,1-*bis*(β-chloroethyl)ethylenimonium ion, is extremely reactive, undergoing hydrolysis or reaction with other groups (e.g., thiosulfate) very rapidly.[5,11a,42] For this reason, the substance has not been isolated. Its formation has been established on the basis of kinetic (see Chapter 20) and analytical studies.[5] The following transformation products of HN3 have been isolated, and their chemical and toxicological properties studied (see Chapter 23): *bis*(β-chloroethyl)-β-hydroxyethylamine picrylsulfonate,[5] 1-β-chloroethyl-1-β-hydroxyethylethylenimonium picrylsulfonate,[5] *bis*(β-hydroxyethyl)-β-chloroethylamine picrylsulfonate[5] and picrate,[42] 1,1-*bis*(β-hydroxyethyl)ethylenimonium picrylsulfonate,[5] and triethanolamine picrylsulfonate.[5] Two cyclic products have also been obtained in low yield. These are the dimer of HN3, N,N,N',N'-*tetrakis*(β-chloroethyl)piperazinium dichloride[42] (synthesis),[27] and N,N'-*bis*(β-chloroethyl)N,N'-*bis*(β-hydroxyethyl)piperazinium dipicrylsulfonate.[5] Like HN1, however, HN3 shows little tendency to form dimeric products, the preponderant reactions being those of hydrolysis.[5] In unbuffered solution the hydrolysis of HN3 slows down and attains a steady state in 48–72 hours.[27b,c,42] The principal product in such an aged solution, as revealed by analytical and isolation data, is *bis*(β-chloroethyl)-β-hydroxyethylamine,[1,27b,42] although *bis*(β-hydroxyethyl)-β-chloroethylamine has also been isolated as a picrate.[22]

19.2.2 Reactions of β-Chloroethyl Groups with Compounds of Biochemical Interest

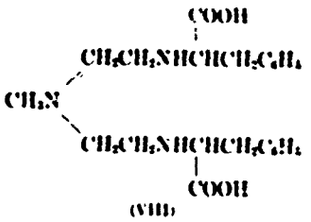
As will be shown in this section, the nitrogen mustards are capable of combining with a wide variety of chemical groupings. In every case in which a reaction has been investigated in detail, however, it has been found that cyclization to the imonium form must occur as the first step. Consequently, when statements are made in the following pages concerning the reactivity of the nitrogen mustards, it is always assumed that it is the imonium form of the vesicant which is actually involved in any reaction. Support for this assumption comes from kinetic studies of the

reaction of the nitrogen mustards with ions such as thiosulfate, thiocyanate, alanine-carboxylate (see Chapter 20). Additional evidence confirming this view was obtained by a study of the reaction of HN2 with the amino group of alanine, glutamic acid, and glycylglycine.[5] It was found that in the reaction with alanine, no amino nitrogen disappears until after the first equivalent of Cl^- has been liberated. The rate of the appearance of Cl^- is unaffected by the presence of alanine. The formation of H^+, however, coincides with the disappearance of amino groups and is faster in the presence of alanine than in its absence. Moreover, it has been shown that alanine and a number of other substances increase the rate of the disappearance of both imonium forms of HN2.[5]

It has been found that the nitrogen mustards react readily with the basic nitrogen atoms in a wide variety of compounds. Thus, reaction has been noted with the primary amino groups of amino acids and peptides,[5] with the secondary and tertiary amino groups of aliphatic amines,[5,28b] and with the nitrogen atom of cyclic amines.[5,28a,b]

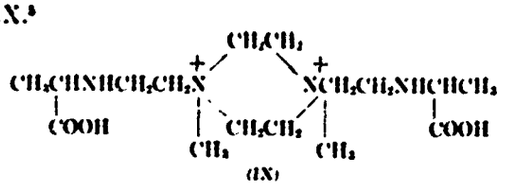
The reaction of the nitrogen mustards (HN1, HN2, and HN3) with the amino groups of amino acids and peptides was studied by determining the extent of the disappearance of amino nitrogen with the aid of the Van Slyke nitrous acid method.[5] The following amino acids and peptides were investigated: glycine, alanine, serine, threonine, glutamic acid, lysine, arginine, histidine, β-alanine, phenylalanine, tryptophane, methionine, and glycylglycine; tyrosineamide acetate and benzoyllysine amide (for HN2 only); leucylglycine and leucylglycylglycine (for HN1 and HN2 only). It was found that the three nitrogen mustards react readily with the amino groups of almost all the substances examined, the extent of the reaction being increased at more alkaline *p*H values. At *p*H 8, the reactivity of the three nitrogen mustards was about the same. Under the conditions employed, between 0.35 and 0.50 equiv of the amino group reacted per equivalent of the β-chloroethyl group. The amino group of peptides was somewhat more reactive than that of simple amino acids. From these experiments it was also concluded that the nitrogen mustards react readily with the imidazole nitrogen of histidine, and that HN3 reacts with the sulfide sulfur of methionine (see p. 396). At *p*H 8, however, the nitrogen vesicants do not appear to react with the phenolic hydroxyl of tyrosine or the indole nitrogen of tryptophane.[5]

The product of the reaction of HN2 with phenylalanine at *p*H 9.5 was isolated and found to have the structure VIII.[5]



(VIII)

In the reaction of alanine with HN2 at *p*H 8, however, the product was believed to have the structure IX.[5]

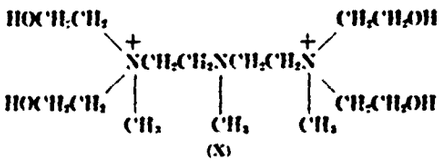


(IX)

The compound was not isolated, but its constitution was surmised on the basis of analytical data (H^+ and Cl^- liberation, disappearance of amino nitrogen, and thiosulfate consumption) obtained in the course of the reaction.

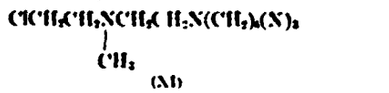
The ability of a given nitrogen mustard to react with secondary or tertiary aliphatic amines, or with cyclic amines, was measured by one or both of two methods. In one method, the thiosulfate method,[28b] the amine and the nitrogen mustard were held in aqueous solution and the unreacted nitrogen mustard determined by thiosulfate titration at any desired time interval. In the second method,[5] the nitrogen mustard, together with alanine and the secondary, tertiary, or cyclic amine under investigation, was allowed to react in aqueous solution at *p*H 8 for 24 hours. At the end of this time the extent of the disappearance of alanine amino nitrogen was measured and compared with the result obtained when the amine under investigation was absent. If the amine being investigated reacted with the nitrogen mustard, the amount of the latter available for reaction with alanine would be decreased and the extent of the disappearance of amino nitrogen would be reduced. Thus, the reaction between a nitrogen mustard and alanine was used to determine whether the nitrogen mustard reacted with a given substance, and further to obtain an estimate of the rate of this reaction relative to the rate of the reaction of the nitrogen mustard with alanine. This second method, called the competition method, is similar in principle to the one used in studying the chemical reactions of H.[28b]

It was found that tertiary amines, both aliphatic and cyclic, react more completely with the nitrogen mustards than do secondary or primary amines.[28b] In the aliphatic series the introduction on the nitrogen of two or more alkyl groups larger than methyl interferes markedly with the reaction.[28a] The replacement of one methyl group by an ethanol or acetic acid radical does not inhibit the reaction.[28b] The product of the reaction of HN2 with methyldiethanolamine was isolated and found to have the structure X.[5,11a]



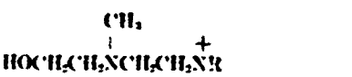
(X)

In the cyclic series, several substances of great reactivity were encountered.[28b] The most reactive compounds appeared to be those containing two or more nitrogen atoms separated by methylene groups, such as diethylene tetramethylene tetramine and hexamethylene tetramine. The main product of the reaction of HN2 with hexamethylene tetramine in water was found to be XI.[28a]



(XI)

From the biochemical point of view, it is of interest that pyridine itself, and the pyridine nitrogen in substances such as pyridoxine, nicotinic acid, and nicotinamide react readily with the nitrogen mustards to form pyridinium derivatives.[5] The compounds formed from HN2 and 1 equiv of pyridine or nicotinic acid have been isolated and found to have the structure XII, where R represents either the pyridine ring or the 3-carboxypyridine group.[5]



(XII)

It should be noted as well that the nitrogen mustards react readily with the imino nitrogen of proline, and with the imidazole nitrogen of acetylhistidine and imidazole.[5] Reaction with thiamin, adenosine, adenylic acid, anserine, carnosine, and sarcosine has also been observed.[5,28b]

Evidence has been obtained that the nitrogen mustards can react with carboxyl groups.[5,10] In the case of HN3, the products of the reaction with sodium acetyldehydrophenylalanine and sodium acetyldehydrophenylalanyldehydrophenylalanine have been isolated and found to be triacyl derivatives of triethanolamine.[5] The reaction products of HN3 with acetate and hippurate have not been isolated, but the extent of esterification (25 per cent, under the conditions employed) has been determined by saponification equivalent.[5] For HN1 and HN2 it has been found that reaction with carboxyl groups does not occur so readily, nor are the reaction products so stable as in the case of HN3. Thus, kinetic studies have shown that the first ethylenimonium ion derived from HN2 reacts with propionate in aqueous solution at *p*H 7.4.[10] The resulting ester of methyldiethanolamine was found to be unstable, however, saponifying with such rapidity that little or no ester could be detected in the reaction mixture after 24 hours. The carbonic acid ester is apparently even more unstable in dilute aqueous solution.[10] Such esters are formed and hydrolyzed at a rate much greater than the direct hydrolysis of the imonium ion of HN2. In effect, therefore, these carboxylate ions catalyze the hydrolysis of the imonium ions.[10] It may be mentioned that no saponifiable esters could be detected after 18-24 hours when HN1 or HN2 were allowed to react with sodium acetate or sodium hippurate.[5] In competition experiments with alanine as the reference substance, no evidence for reaction of acetate with HN2 was found.[5] It appeared, however, that hippurate reacted slightly, and that carbobenzoxyglutamic acid and carbobenzoxyaspartic acid reacted appreciably, with HN2.[5] In the latter cases it seems probable that it is the γ-carboxyl of glutamic acid and the β-carboxyl of aspartic acid which are involved. In contrast to HN2, carbobenzoxyglutamic acid does not compete at all with alanine for reaction with HN1. The results summarized above make it appear probable that the order of reactivity of the nitrogen mustards toward carboxyl groups is: HN3 > HN2 > HN1.[5]

There is abundant evidence to indicate that all of the nitrogen mustards react readily with sulfhydryl groups.[5,10,22] The reactions of HN1, HN2, and HN3 with thiosulfate have received particular attention.[5,10,58] (For the kinetics of the reaction, see Chapter 20.) The reactions of HN1, HN2, and HN3 with thiosulfate proceed so rapidly that even in dilute solution the imonium ions combine quantitatively with thiosulfate and hydrolysis is suppressed. Reference to the high reactivity of thiosulfate has already been made (p. 391). HN1 and HN2 combine with

2 equiv, and HN3 with 3 equiv of thiosulfate. The product of the reaction, the Bunte salt, has been isolated in each case.[5] The behavior of thiocyanate is qualitatively similar to that of thiosulfate.[10] The nitrogen mustards also react very readily with the sulfhydryl groups of cysteine, glutathione, and *bis*(β-mercaptoethyl) sulfide.[22] The product of the reaction between HN2 and cysteine was isolated and found to be the *bis*-S-cysteinyl derivative.[22] With potassium toluenethiosulfonate, HN2 gives the corresponding *bis*-thiosulfonate ester.[5]

As a result of studies with free amino acids, it was stated on p. 394 that HN3 reacts with the sulfur of methionine. However, the evidence concerning the reactivity of HN1 and HN2 toward methionine sulfur is equivocal.[5] On the other hand, by utilizing the competition method, it could be shown definitely that all three of the nitrogen mustards combined with the sulfur of thiodiglycol, presumably with the formation of a sulfonium salt.[5] The nitrogen mustards also react with inorganic sulfides, polysulfides, and bisulfite.[41,59]

In view of the importance of phosphate and phosphorylated compounds to the economy of the living cell, it is of interest that the nitrogen mustards have been found to react with both inorganic and organic phosphates.[5,27b] The extent of the reaction was measured by determination of inorganic phosphate,[5,27b] and by the alanine competition method.[27b] The following compounds were found to react with HN2: Na_2HPO_4, $Na_4P_2O_7$, sodium glycerophosphate, fructose-1- and fructose-6-phosphate, glucose-3- and glucose-6-phosphate, cytidine diphosphate, and adenosine triphosphate. Theophylline glucoside and desoxyribose were inactive.

When one of the β-chloroethyl groups of a nitrogen mustard reacts with a given functional group, it is to be expected that the chemical nature of the group which is introduced into the nitrogen mustard will influence the reactivity of the second chloroethyl group. The validity of this supposition was supported by experiments with monosubstituted derivatives of HN1 and HN2.[5,12] The derivatives were prepared by allowing the chloroethylethylenimonium picrylsulfonate of HN1 or HN2 to react in acetone solution with the desired compound. The products were isolated as picrylsulfonates. The following monosubstituted derivatives were examined: the pyridine and methyldiethanolamine derivatives of HN1 and HN2, and the nicotinic acid, hexamethylene tetramine, and thiodiglycol derivatives of HN2. It was found that the monosubstituted derivatives of both HN1 and HN2 reacted more slowly with aqueous thiosulfate than did the corresponding chlorohydrins. Moreover, the HN1 derivatives consumed thiosulfate more rapidly than did the corresponding HN2 derivatives. It was also found that during hydrolysis, Cl^- was liberated more slowly from the monosubstituted HN2 derivatives than was the case with HN2 chlorohydrin.

On the basis of the work summarized in this section it is apparent that the nitrogen mustards can react with a wide variety of cell constituents. The reactivity of these vesicants with amino groups, sulfhydryl groups, carboxyl groups, sulfide groups, and imidazole groups indicates that the nitrogen mustards *in vivo* may attack free amino acids, peptides, and proteins (including, of course, enzymes and hormones) in a number of ways. The vesicants may also react with essential coenzymes such as nicotinamide, pyridoxine, and thiamin. The ability of the nitrogen mustards to combine with organic and inorganic phosphate is of biochemical interest and points to the possibility that the vesicants may interfere with normal cellular activity not only by combining with cell catalysts but by reacting with essential substrates as well. Reaction with carboxyl groups could also operate in this manner. It should be mentioned that nucleic acids contain both phosphate and amino groups, and hence these substances also may be acted upon by the nitrogen mustards.

In view of the wide range of chemical groups which may enter into combination with the nitrogen mustards, it is not surprising that these substances are potent cell poisons. Moreover, on the basis of current knowledge it would appear that the nature of the chemical linkages formed is such that cleavage of the vesicant residue under conditions compatible with cell life seems unlikely. Although systematic investigations of the stability of numerous nitrogen mustard derivatives are lacking, no indications of instability have been reported, with the exception of a few of the esters referred to above. The stability of the compounds not specifically investigated may be inferred by analogy from the nature of the linkages involved.

19.2.3 N Oxides of Nitrogen Mustards

The nitrogen mustards are rapidly oxidized by peracids in aqueous solution at weakly alkaline *p*H values.[5] In acid solution the oxidation is much slower. All the products of the reactions, the N oxides of HN1, HN2, and HN3, have been isolated as their

hydrochlorides.[5] The high yield obtained (78–85 per cent) indicates that oxidation of the nitrogen atom proceeds much more rapidly than does hydrolysis of the β-chloroethyl groups. The stability of the β-chloroethyl groups of the N oxides was investigated by measuring the liberation of H^+ and Cl^- and the consumption of thiosulfate in bicarbonate solution.[5] It was found that both HN2 and HN3 N oxides liberate Cl^- and H^+ and consume thiosulfate, HN3 N oxide being the more reactive. The reactions are much slower than those observed with the parent nitrogen mustards. The final products of the hydrolysis, which have not been identified with certainty, do not consume thiosulfate.

19.3 CHEMICAL REACTIONS OF *bis*-(β-CHLOROETHYL) SULFIDE (H)

19.3.1 Transformations in Water

The transformations undergone by *bis*(β-chloroethyl) sulfide (H) in water are given in Figure 2.[10,56b] The sequence of reactions given in the figure is similar in many respects to that given for HN2 in Figure 1, and support for Figure 2 is derived from the same three types of experimental evidence presented to substantiate Figure 1; namely, kinetic data, analytical data on hydrolysates of H (H^+ and Cl^- liberation, etc.), and data obtained by the isolation of the compounds given and the study of their properties. Mention should be made, however, of three notable differences between the behavior of H and that of the nitrogen mustards. In the first place, the cyclic ethylenesulfonium ions, XIII and XV, which according to one theory are formed from H and its chlorohydrin (CH, β-chloroethyl β-hydroxyethyl sulfide, XIV), are extremely unstable, do not accumulate in solution, and hence have never been isolated. Their existence is predicated on indirect evidence derived largely from kinetic investigations (see Chapter 20). In the second place, dithiane sulfonium compounds have not been detected in hydrolysates of H. It will be recalled, however, that cyclic piperazinium derivatives are sometimes formed during the hydrolysis of

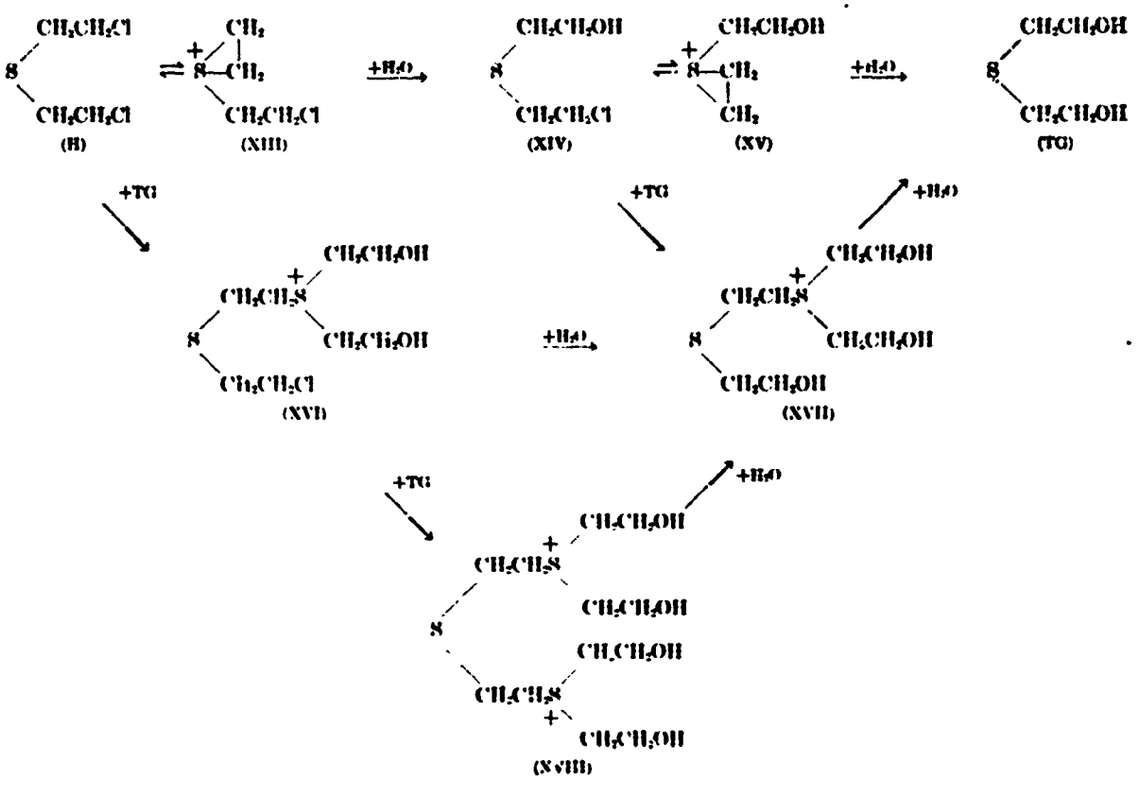


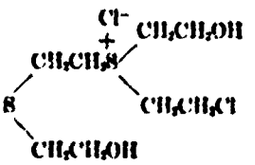
FIGURE 2. Transformations of *bis*(β-chloroethyl) sulfide (H) in water.

the nitrogen mustards. In the third place, the linear sulfonium salts formed from H (i.e., compounds XVII and XVIII), are reactive, toxic substances, whereas the analogous quaternary ammonium compounds formed in the case of the nitrogen mustards are stable and relatively nontoxic.

The kinetics of the hydrolysis of H in very dilute aqueous solution were studied in World War I, and these studies have been greatly extended in World War II (see Chapter 20). In dilute solutions H hydrolyzes exclusively to thiodiglycol [*bis*(β-hydroxyethyl) sulfide, TG] and HCl, with the intermediate formation of the sulfonium ions XIII and XV, and of CH (XIV) (see Chapter 20). On the other hand, it has been demonstrated[44] that when the ratio of water to H is small (about 3/1), only a small quantity of TG and HCl are formed, most of the H being converted to a mixture of sulfonium chlorides. These experiments, however, were performed under conditions quite dissimilar to those obtaining when H reacts with water under physiological conditions.

There are, however, many data which indicate that sulfonium salts are formed when H is hydrolyzed with moderate quantities of water at room temperature.[4,24,25,26,36,54b] For example, when H was shaken with 50 volumes of water for 24 hours at 20 C, the resulting clear solution was toxic and contained only about 78 per cent of the theoretical amount of HCl to be expected on complete hydrolysis of H.[4] On heating the neutralized solution at 100 C for 2 hours, however, the remainder of the theoretically possible HCl was liberated, and the toxicity was destroyed.[4,25] As will be shown later, the sulfonium salts formed during the hydrolysis of H decompose on heating at 100 C in aqueous solution, with the formation of 1 equiv of acid for each sulfonium group. Hence, the amount of acid produced on heating an hydrolysate at 100 C is an index of the extent of sulfonium salt formation. On this basis, about 22 per cent of the chlorine of the original H is found as sulfonium chloride after hydrolysis of H with 50 volumes of water at room temperature.[4] If the ratio of water to H is increased to 200 volumes, the extent of sulfonium salt formation drops to about 16 per cent; if 1,000 volumes of water are used, the extent of sulfonium salt formation falls to about 5 per cent.[4]

Support for Figure 2 has also been derived by isolation of many of the intermediates listed and a study of their properties. Thus, CH (XIV) has been isolated from partially hydrolyzed aqueous solutions of H.[29a,34d] Unchanged H was removed by extraction with cyclohexane, purified kerosene, or petroleum ether, and the aqueous solution of CH and sulfonium salts was then extracted with chloroform to remove the CH. The CH may be recovered by removal of the chloroform *in vacuo*. CH has been synthesized by reaction of thionyl chloride with TG under carefully controlled conditions,[29b] and from vinyl chloride and monothioglycol.[34a] In the isolated form CH is quite unstable at room temperature, spontaneously undergoing partial polymerization on standing in alcoholic solution or in the absence of solvent. The product formed under these conditions has been stated to be the di-CH sulfonium salt, XIX.[34d]



(XIX)

When frozen and stored at dry ice temperatures, however, CH is stable.[17a] In isopropyl ether or chloroform solution CH also is stable. Acetone, on the other hand, appears to promote polymerization.[34d,h]

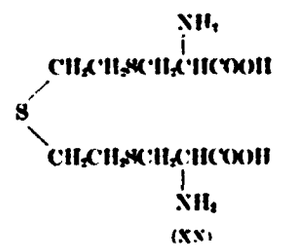
In dilute aqueous solution, freshly prepared CH hydrolyzes to TG and HCl at a unimolecular rate which is 40–50 per cent faster than that observed for H.[29a,34d,h] Samples of CH which have been aged and have undergone polymerization, however, show an initially more rapid reaction followed by the normal hydrolytic reaction, followed in turn by a very much slower reaction.[34d,h] This sequence of events is interpreted to indicate conversion during aging of some CH to give XIX, which hydrolyzes rapidly to XVII, the latter in turn decomposing slowly to TG. Moreover, on hydrolysis of pure CH (0.11*M*) in aqueous solution, the liberation of H^+ is slower than the liberation of Cl^-, indicating the presence in the hydrolysis mixture of considerable quantities of sulfonium chlorides.[34] The sulfonium chlorides might contain an ethyleneosulfonium ring, as in XV, or they might be of the type represented by XVII. Differentiation of these two types of sulfonium compounds can be made on the basis of the thiosulfate reaction. Compounds such as XV should react quantitatively with thiosulfate in 10 minutes, whereas sulfonium salts of the type XVII should not react measurably with thiosulfate in this time interval. If XV were present in the hydrolysate, therefore, the 10-minute thiosulfate titer of an hydrolysate at any given time should be

greater than the amount of carbon-bound chlorine (i.e., unchanged CH) remaining in the solution. Actually it was found to be slightly less, indicating that the thiosulfate consumption was all attributable to unchanged CH and that XV did not accumulate in the hydrolysate to a measurable extent.[16] The sulfonium compound present in hydrolysates of CH is almost certainly XVII, which is formed by reaction of CH with TG. It has been shown that reaction between CH and TG can occur in aqueous solution.[16] Moreover, when CH hydrolyzes in the presence of TG, H^+ formation is markedly repressed, whereas Cl^- liberation proceeds in accordance with the kinetics of competition (see Chapter 20).

The sulfonium salts XVI, XVII, and XVIII have been subject to much study.[4,14,16,48 54b 64] Compound XVI has not been isolated from hydrolysates of H, but its existence as a precursor of XVIII can scarcely be doubted. In the first place, it is hardly conceivable that 2 molecules of TG could react simultaneously with 1 molecule of H. In addition, XVI has been synthesized by allowing equivalent molar quantities of H and TG to react in ethanol and has been found to possess the properties expected.[48,48] Thus the chloride of XVI was an unstable oil which, on standing, decomposed to yield XVIII and to regenerate some H.[48] The picrylsulfonate of XVI was isolated in crystalline form, however, and proved to be quite stable.[16] In aqueous methyl Cellosolve, the picrylsulfonate of XVI decomposes in two stages with the overall liberation of 1 equiv of chloride ion and nearly 2 equiv of acid. The first stage, in which 1 equiv of chloride and 1 equiv of acid are liberated, has a half-life time of about 3 hours; whereas the second stage, in which the second equivalent of acid is liberated, has a half-life time of about 2 days.[16] At the end of the first-stage reaction, the picrylsulfonate of XVII was isolated from the reaction mixture, thus supporting the reaction sequence from XVI to XVII as given in Figure 2.[16,48]

It was also found that in aqueous solution the picrylsulfonate of XVI reacted with TG to yield XVIII, as would be predicted from Figure 2.[16] It was of some interest to note that XVI picrylsulfonate reacted readily with aqueous thiosulfate.[16] The reaction proceeded in two stages, 1 equiv of thiosulfate being consumed in about 6 hours, whereas only 0.6 additional equiv of thiosulfate was consumed after 71 hours. The first stage of the reaction undoubtedly involves the β-chloroethyl group and occurs at a rate comparable with the liberation of Cl^- in the absence of thiosulfate. The second stage of the reaction is comparable in rate to the liberation of the second equivalent of acid in the absence of thiosulfate, and probably involves the sulfonium group of XVI. The ability of sulfonium compounds to decompose with the liberation of thiosulfate-reactive groups is discussed below.

The sulfonium compounds XVII and XVIII have both been isolated from hydrolysates of H.[4,14,24] After hydrolysis with 50 volumes of water 26 per cent of the original H was recovered as the picrylsulfonate of XVII, and 16 per cent as the dichloride of XVIII. The total amount of sulfonium compounds isolated represents about 50 per cent of the amount of sulfonium ion estimated to be present in the hydrolysate.[14] Compound XVIII was also synthesized in good yield by shaking H at room temperature with an aqueous solution of TG.[4] The reaction proceeds more readily in water than in nonaqueous or partially aqueous solutions. With respect to the chemical properties of XVIII, this compound was found to be 30 per cent decomposed with the liberation of acid upon standing in dilute aqueous solution for 3 weeks.[64] It is readily decomposed when heated in dilute aqueous solution.[4,23,64] At *p*H 8.9 or 9.9 at 3 C°, the salt liberates no acid in 24 hours, whereas in 0.33 *N* NaOH 25 per cent of the theoretical acid is liberated in this period of time.[4] When incubated in aqueous bicarbonate at 37 C and *p*H 7.6, a slow liberation of acid occurs (1 equiv in 90 hours).[16,48] If thiosulfate is also present in the reaction mixture, a reaction occurs which consumes thiosulfate.[16] The speed of this reaction is only slightly greater than the liberation of acid from XVIII in the absence of thiosulfate. In the presence of cysteine, XVIII reacts at 37 C° to form the *bis*-S-cysteinyl derivative of H (XX).[16]



(XX)

The other product of the reaction is probably TG, although it has not been isolated. The formation of XX, coupled with the observations reported above, make it appear that the sulfonium groups of XVIII possess, to a lesser degree, some of the reactive al-

kylating properties associated with the β-chloroethyl groups of H.[18] The same considerations also hold for the sulfonium groups of XVI and XVII. As will be shown in Chapter 22, all of these sulfonium salts, particularly XVI, possess a noteworthy toxicity. It appears probable that this toxicity may be a reflection of the ability of these salts to decompose under physiological conditions with the formation of reactive, toxic products.[18] Whether or not sulfonium salts of the types given in Figure 2 are actually formed from H *in vivo* is still undecided. It remains possible, therefore, that some of the physiological effects of H are a consequence of the properties of these sulfonium compounds.

19.3.2 Reactions of β-Chloroethyl Groups with Compounds of Biochemical Interest

Until the work described in this section had been performed, the chemical basis for the remarkable physiological activity of H remained obscure. H was recognized to be a general cell poison, but the manner in which it might exert its toxic effects was not appreciated. Among the many theories[50] proposed to account for the toxicity of H, two may be mentioned. According to one theory, the HCl generated within cells by hydrolysis of H was responsible for its vesicant action. A second theory postulated the oxidation of H *in vivo* to the sulfone,[51,66] the sulfone being considered as the vesicant agent. The first theory was finally abandoned when it was found that the amounts of H required to produce toxic effects are so small that the HCl produced on hydrolysis would be insufficient to cause appreciable changes in *p*H. The second theory is no longer looked upon with favor for several reasons. In the first place, it has been calculated that the potential required to oxidize H to the sulfone is greater than that to be anticipated in normal cells.[51] In the second place, it has been found that animals rendered hypersensitive to H are not hypersensitive to the sulfone.[51] Finally, the sulfone theory has been discarded because it no longer is required to explain the facts. Early workers had not appreciated the great chemical reactivity of the β-chloroethyl groups of H under physiological conditions of solvent, *p*H, and temperature. Prior to World War II only a few reactions involving the β-chloroethyl groups of H had been reported. These reactions, with amines,[61,66,71] and with alkali sulfides[69] and cyanides,[61] had been studied for the most part in nonaqueous solvents, and under drastic conditions of *p*H and temperature. In the earlier work, therefore, H sulfone appeared to be a more reactive substance than did H.

It has now been demonstrated that H is capable of reacting with a wide variety of functional groups.[2,34c] The reactions have been shown to involve replacement of the chlorine atoms of H; that is, to be alkylation reactions. As a result of kinetic investigations (see Chapter 20) the following facts relative to the alkylation reactions of H have been established: (1) The rate of the reaction of H with various substances (anions) is, like the hydrolysis rate, unimolecular. (2) The rate of reaction of H is a constant dependent upon solvent and temperature, and independent of the substance with which H is reacting. (3) The rate of the reaction is markedly slowed by nonpolar solvents. In order to interpret these facts it has been postulated that H reacts in two steps.[2,34c] In the first step one of its β-chloroethyl groups becomes activated. This activation process is measurably slow and occurs only in the presence of water or other polar solvents. It has variously been ascribed to carbonium [34c] or ethylenesulfonium [2,38] ion formation. The second step is immeasurably rapid and results in the reaction product. The first step, therefore, is the rate-determining one. However, various compounds differ in their affinities for the activated H molecule. Thus, in very dilute aqueous solutions hydrolysis to thiodiglycol (TG) occurs almost exclusively. If other substances are present in solution, however, they may compete with hydroxyl ions for the activated H molecule. The extent of the success of a substance in competing with water for activated H depends upon the relative availability of the electrons of the competing substance.[2,34c] The relative affinities of various substances in competing with water for activated H have been termed "competition factors." [34c] A list of the competition factors for a number of substances is given in Table 5.

As a consequence of the mechanism outlined above, several conclusions become apparent. Since the rate of reaction of H is fixed, for given conditions, the rate constant for the disappearance of H is independent of the nature of the substance with which it is reacting.[2,34c] Thus, not one of the substances listed in Table 5 causes mustard to react more rapidly than it is hydrolyzed by water. The degrees of reaction with different reagents, therefore, are in proportion to the products of their concentrations and their competition factors.[2,34c] In mixtures, therefore, other things being equal, groups of high competition factor

will in effect react first. Since there is no evidence to indicate that II reacts *in vivo* by any mechanism other than the one outlined above, it appears that *in vivo* reaction of II occurs in the aqueous phase by substitution of the chlorine atom.[2,51]

According to one hypothesis, the ease with which a given anion (not necessarily an acid) can react with II is a function of the electron availability of the anion in question.[2] The greater the electron availability, the more readily should the anion react and the higher should be the competition factor. The evidence supporting this hypothesis has been documented in detail,[2] and need not be given here. Suffice it to say that with the aid of this theory it is possible to give a rational explanation of the competition factor data given in Table 5, and to predict roughly the competition factors of anions. Among the facts elucidated by the hypothesis are the notably high competition factors of sulfur compounds in general, such as thiophosphates, thiophosphonates, thioacids, thiophenols, and thiols. The data given in Table 5 for carboxylic acids finds rational interpretation in terms of the influence of other functional groups in the molecule upon the electron availability of the carboxyl groups. Similar analyses have been carried out for phenols, enols, amines, and inorganic ions such as phosphate.[2]

From the biochemical point of view, the groups listed in Table 5 which are of most interest are the sulfhydryl group, as in cysteine or glutathione; the pyrophosphate and phosphate ions; the organic phosphate compounds such as adenylic acid or glycerophosphate; the nitrogen atoms of pyridine itself,[4,15,68] and hence presumably of nicotinamide and pyridoxine; carboxyl groups as in citrate, oxalate, fumarate, acetate, and pyruvate; the imidazole group of histidine; the sulfide sulfur of TG and methionine, and the amino groups of amino acids, peptides, purines and pyrimidines. These various reactions will be considered in more detail.

Of all the naturally occurring compounds listed in Table 5, those containing sulfhydryl groups have the highest competition factors. Notable in this respect is ergothionine which, though not presently known to be widely distributed, has been found in nature. It will be noted that cysteine ethyl ester has a higher competition factor than cysteine. It has been observed,[22] moreover, that glutathione is less reactive than cysteine. The compound formed from II and 2 equiv of cysteine has been isolated[22] and found to have the structure XX given on page 399. Products of the reaction in boiling alcohol of II with the sodium salts of thiophenol and alkyl mercaptans have been prepared and found to have the general structure $(RSCH_2CH_2)_2S$, where R may be an alkyl or a phenyl group.[58] The stability of compounds of this type (of which the cysteine product is one) should be relatively great. In general, cleavage of a -C-S-C- linkage requires drastic conditions. It has been found, however, that the linkage is more labile in certain derivatives of II- sulfone (or divinyl sulfone). For example, *bis*(cysteinylethyl) sulfone, after treatment with silver or mercury salts at mildly alkaline *p*H values, gave a positive nitroprusside test for sulfhydryl groups. This finding would indicate that cleavage of the C-S-C-linkage had occurred (see also page 409). With *bis*(cysteinylethyl) sulfide, however, a similar reaction does not seem to occur with so great ease.[59,60] It remains true, therefore, that so far as we know now, the products of the reaction of II with sulfhydryl compounds are stable under conditions of *p*H and temperature compatible with cell life.

Except for the data given in Table 5, the reaction of II with organic or inorganic phosphates has not been studied in great detail. The reaction of II with inorganic phosphate has been investigated,[27b] and the phosphate ester of thiodiglycol has been synthesized.[58] The high competition factors of phosphates, however, coupled with their wide distribution and important functions in the animal organism, render these reactions of great biochemical interest.

The reaction of II with pyridine and its derivatives has been studied somewhat more extensively.[4,15,68] Thus, it has been demonstrated that II reacts with nicotinic acid and its amide to form pyridinium compounds.[4] The product of the reaction of II with pyridine has been isolated as the dichloride[68] and as the dipicrylsulfonate and found to be the *bis*(pyridinium) compound.[15,58] This substance, in contrast to the analogous sulfone derivative, was found to be stable in aqueous solution at *p*H 7.5 and 25°C.[15] No acid was liberated, and the substance did not react with thiosulfate or the sulfhydryl group of cysteine. Attempts to prepare the methyl sulfonium salt by reaction of *bis*(β-pyridiniumethyl) sulfide with methyl iodide were unsuccessful.[15]

Evidence has been secured (see Chapter 21) that both *in vivo* and *in vitro* II reacts with the carboxyl groups of proteins. For this reason the reaction of II with simple carboxylic acids to form esters of TG has been the subject of considerable study. It has

TABLE 5. Competition factors* of various substances for II.

Substance	Competition factor	Reference
Dithiophosphate ion	130,000	54c
Ethane dithiophosphonate ion	120,000	54b,c
Hexane dithiophosphonate ion	120,000	54b
Methane dithiophosphonate ion	105,000	54b,c
Butyl dithiophosphate ion	74,000	54b,c
Ethyl dithiophosphate ion	63,000	54b,c
β-Aminothiophenol	50,000	54b,c
Thioformate ion	50,000	47
Pentaethylenedithiocarbamate	44,000	47
Dimethyldithiocarbamate	40,300	48
Ethane monothiophosphate ion	39,000 (21,900)	54b,c (48)
Monothiophosphate ion	38,000 (12,500)	54c (48)
Butane monothiophosphate ion	36,000	54b,c
Diethanol dithiocarbamate	34,000 (20,000)	54c (48)
Diethyl dithiocarbamate	33,000	54a,b,c
Methane monothiophosphonate ion	30,000	54b
Methylphenyldithiocarbamate	28,900	48
Thiosulfate ion	27,000	2, 54a,c
Chloroethyl-β-dithiophosphonoethyl sulfide	26,000	54c
Methylethanoldithiocarbamate	22,600	48
Morpholinodithiocarbamate	22,200	48
Ethyl xanthate	20,000	54a,b,c
Octyl xanthate	10,500	54c
Ethyl monothiocarbonate ion	9,300	54b,c
Hydroxyl ion	8,000	54c
Choline xanthate	7,800	54b,c
Diethane dithiophosphonate ion	6,700	54c
Dithioacetate ion	5,200	54a,c
Dithiovalerate ion	5,100	54c
Dimethane dithiophosphonate ion	4,900	54c
Thioglucose	3,200	54b
Diethyl dithiophosphonate ion	2,600 (5,700)	54b (47)
Cysteine ethyl ester	1,700	54b,c
Sulfite ion	1,500	2
Thioglycol ester	1,350	54a,b,c
Ergothionine	1,220	21, 48
Mercaptomalonic ester	1,050	54c
Cysteine	1,050	54a,c
Hydrosulfide ion	1,050	54c
t-Butyl trithiocarbonate ion	1,050	54c
Mercaptopyruvate ion	1,000	54b,c
Ethylene mercaptan	880	54a,b,c
Dimercaptotoluene	780	54a,c
2,3-Dimercaptopropanol	780	54c
Aniline	760	11
Hexamethylene tetramine	740	8
Thiomalic ester	700	54c
Thiocyanate ion	670	2, 54c
Iodide ion	660	54b,c
p-Toluenethiophosphonate ion	510	54b
2-Mercapto thiazole	500	54c
Thioglycolic acid	450	2
Thiohydracrylic acid	410	2
β-Mercaptoethanol	400	2
Methylamine	390 (pH 13)	11
n-Butanethiosulfonate ion	390	2
p-Toluenethiosulfonate ion	380	2
Butyl mercaptan	300	2
Ethyl mercaptan	280	2
Methionine	260	11
Veronal	260 (pH 9.9)	11
Veronal	4.5 (pH 1.3)	11
Dimethylamine	255 (pH 13)	11
Cystine	240 (pH 13)	11
Tryptophane	210 (pH 13)	11
Pyrophosphate ion	160	54c
Thiourea	150	54b,c
Lysine	147 (pH 13)	11
Desoxycholate ion	110	54c
Imidazole	110	11
Bicarbonate ion	83	54c
Citrate ion	83	2
Adenylate ion	75	54c
Phosphate ion	75	54c
Phenol	75 (pH 13)	11
Tricarballylic acid	73	2
Histidine	71 (pH 13)	11
Histidine	67 (pH 7)	54c, 11
Adenosine	56	54c
Glycerophosphate ion	54	54c
Pyridine	54	54c
Citraconate ion	49	2
Fumarate ion	44	2, 54a,c
Oxalate ion	44	2, 54a,c
Maleate ion	43	2
Arginine	42 (pH 7)	11
Cyclohexane-1,1-diacetate ion	35	2
Malonate ion	32	2
bis(β-Hydroxyethyl) sulfide (thiodiglycol)	30	2
Succinate ion	28	2
p-Toluenesulfinate ion	25	2
Itaconate ion	22.4	2
Chloride ion	21	23, 54a,c
Adipate ion	20.6	2
Glutarate ion	20.4	2
Muconate ion	19.2	2
Leucylglycylglycine	19	54c
Ascorbate ion	19	54c
Alanylalanine	18	54c
Tartrate ion	16.4	2
Tyrosine	16.0	54a,c
Malate ion	16.0	2
p-Aminobenzene sulfinic acid	15.0	2
Benzamidine	14	54c
Mucate ion	12.1	2
Acetylalanine	10.5	54c
Hydracrylate ion	10.3	2
Glutamate ion	8.6	2
Levulinate ion	8.5	2
Acetate ion	8.5	2, 11, 54a,c

* An attempt has been made to render this table complete. The literature is so scattered, however, that omissions doubtless have been made. A complete list of competition factors determined prior to December 1942, has been compiled,[48] and has been of great service in assembling this table.

TABLE 5 (*Continued*)

Substance	Competition factor	Reference
Methylamine hydrochloride	8.5 (pH 1)	11
Sulfate ion	7.3	2, 54c
Triethylamine	6.7	54a,c
Crotonate ion	6.1	2
p-Nitrobenzoate ion	4.3	2
Tyrosine (amino group)	4.0	54a
Pyruvate ion	3.4	2
Monochloroacetate ion	3.0	2
Formate ion	3.0	2
Alanine (carboxyl group)	2	54a
Alanine (amino group)	2	54a
Diacetone alcohol	2	54a
Acetomalonate ion	2	54a
Ethyl citrate ion	2	54a
Propionate ion	1.8	2
Glycine	1.6	2, 54a
Acetamide	1.5	11
Sodium formaldehyde sulfoxylate	1.4	2
Picrate ion	1.2	2
Lactate ion	1.1	2
Nitrate ion	0.2	2
Glucose	0	2
p-Toluenesulfonate	0	2
n-Butyl sulfonate	0	2
n-Butyl thiosulfate	0	2

been found in the case of acetate that H reacts only with the carboxylate anion, so that at low *p*H values ester formation is negligible.[22] At physiological *p*H, however, all the acids which have been investigated will be present largely as the dissociated salt, so that *in vivo* reactions of II with carboxyl groups is a likely theoretical possibility.[2,4]

The electron-donating strength of a group R is an important factor in determining the dissociation constant of a carboxylic acid, RCOOH.[2] The stronger is the electron-donating strength, the greater will be the tendency of the anion, $RCOO^-$, to form a covalent bond with hydrogen, and the weaker will be the acid. The dissociation constants of organic acids are, therefore, useful guides in assessing competition factors.[2] However, no exact parallelism exists because of the influence of other factors which do not affect dissociation constants and competition factors to the same extent.[2] This fact is brought out by the data in Table 6,[2] in which the competition factors and dissociation constants are included for comparison. It may be noted by a comparison of the data for lactic and pyruvic acids with those for hydracrylic and levulinic acids that the competition factors are influenced by the distance from the carboxylate ion of a group responsible for decreasing the electron-donating strength of the anion.[2] A comparatively powerful substituent group is the free carboxylate ion, which operates in determining the second dissociation constant (K_2) of a dibasic acid.[2] The figures in Table 6 on adipic, glutaric, succinic, malonic, and oxalic acids indicate the rise in competition factor as the carboxyl groups come nearer together. The conjugated system present in maleic, fumaric, and citraconic acids is an efficient mechanism for transmitting the effect of one carboxyl to the other.[2] These acid residues would be expected to have competition factors equal among themselves and equal to oxalic acid. As may be noted in the table, this is found to be the case. Among the hydroxy dibasic acids, the same qualitative agreement exists between the expected electron-attracting effect of the substituent group and the value of the competition factor, but there is no correlation between K_2 and the competition factor. The relatively high competition factors of citric (83) and tricarballylic (73) acids may be ex-

TABLE 6. Competition factors and dissociation constants of carboxylic acids.[2]

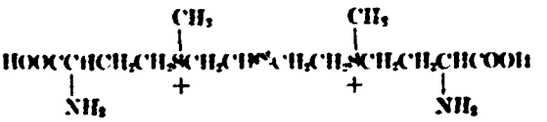
Acid	Competition factor	Dissociation constant
		$K \times 10^5$
Acetic	8.5	0.17
Crotonic	6.1	0.22
Lactic	1.1	1.40
Formic	3.0	2.04
Chloroacetic	3.0	18.1
Aminoacetic (glycine)	1.6	45.0
Pyruvic	3.4	56.0
Hydracrylic	10.3	0.3
Levulinic	8.5	0.2
		$K_2 \times 10^5$
Adipic	10.8	3.87
Glutaric	10.2	3.80
Succinic	13.8	3.33
Malonic	16.0	2.03
Oxalic	21.8	49.0
Maleic	21.5	0.26
Fumaric	21.8	22.0
Citraconic	24.3	0.39
Itaconic	11.4	2.2
Malic	8.0	7.5
d-Tartaric	8.2	43.0
Mucic	6.1	....
Muconic	9.5	....

plained by the proximity of the carboxylate and hydroxycarboxylate anions to a given carboxyl, thus increasing the electron-donating strength of the latter.[2]

The following esters of thiodiglycol (TG) have been prepared: the diformate,[62] dipropionate,[62] dibutyrate,[62] divalerate,[62] dicaprate,[62] di-*p*-nitrobenzoate,[74] diacetate,[2,4,62,63] diisippurate,[4] and disalicylate.[4] All but the last three of the substances listed were prepared under various drastic conditions so that their isolation is of little significance to the present discussion. The last three compounds were prepared by reacting H with an aqueous solution of the sodium salts of the acids. Under similar conditions the formation of esters was noted from H and the sodium salts of citric, succinic, and stearic acids, although the reaction products were not isolated.[4] Thiodiglycol esters of acetyldehydrophenylalanine and acetyldehydrophenylalanyldehydrophenylalanine have also been prepared.[4]

Certain facts relative to the stability of thiodiglycol diacetate have been noted.[4] At 100 C in neutral aqueous solution the compound is not saponified in 2 hours, but in 0.05*N* NaOH at 4 C, saponification is complete within 1 hour. At *p*H 8.9 and 3 C, no saponification was noted in 24 hours, whereas if the *p*H was raised to 9.9 or 12.5, saponification in 24 hours was 5 per cent and 100 per cent complete, respectively.[4]

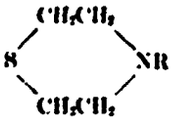
The ease with which H can react with the sulfide sulfur of compounds such as TG or methionine may be judged by the competition factors of these substances (see Table 5). The reactions of H with TG have already been discussed. With methionine, H gives a sulfonium salt of the structure XXI.[4]



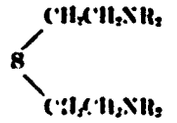
(XXI)

This compound has been isolated as its tetraazobenzenesulfonate. On heating in aqueous solution the sulfonium salt decomposes with the liberation of acid.[4] The products of the decomposition are methionine, which is regenerated in large amounts, and γ-hydroxy-α-aminobutyric acid and *bis*(methylthioethyl) sulfide, both of which are obtained in relatively low yield.[4] The formation of the latter two compounds serves, however, to establish the structure of the original sulfonium salt as that given above. Reaction of H with carbobenzoxymethionineamide has also been noted.[4]

The ability of H to react with amines has been long known. As far back as 1912 the reactions of H with aniline and benzylamine were studied and the products of the reactions identified.[61] Subsequently the investigations were widened to include numerous compounds bearing amino groups. With the primary amines in hot alcoholic solutions, thiazans (i.e., thiomorpholines) of the general type



were obtained, in which R may be an alkyl radical (methyl, ethyl, propyl, butyl, amyl, etc.) or a phenyl or benzyl group.[2,61,63,66,71] With secondary amines under the same conditions, substances of the structure



have been obtained, where R is an alkyl group.[66] With piperidine and pyridine the *bis*(piperidinium) or pyridinium ethyl sulfides were isolated.[4,15,66] In the reaction of H with glycine ethyl ester in hot alcoholic solution, three different compounds have been obtained. These are sulfido-*bis*(β-ethylaminoethyl acetate),[60] 1,4-thiazan-3-acetic acid,[55,60] and β-hydroxyethylsulfide-β-ethylaminoacetic acid.[55]

Under milder experimental conditions which are of greater physiological interest, the reaction of H with *n*-propylamine and diethylamine led to a mixture of products.[2] With triethanolamine, the *bis*(triethanolammonium) derivative was isolated.[4] By following the disappearance of amino nitrogen in the Van Slyke apparatus, it has been demonstrated that H reacts with the amino groups of amino acids and peptides in aqueous solution at *p*H 8 and room temperature. H also reacts with the amino groups of brain cephalins.[57] It should be pointed out that under physiological conditions (*p*H 7.35) most amines are too highly dissociated to be present to a large extent as the free base. There are, therefore, limitations on the probability of H reacting with amino groups *in vivo*.[2]

There is much indirect evidence to indicate that H may react with the imidazole group of histidine. The

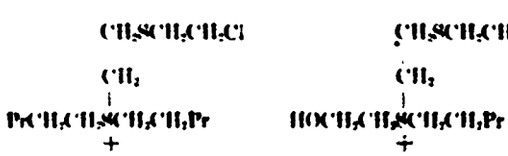
high competition factor of histidine as compared to other amino acids is one indication. Additional evidence is provided by the decrease in color given by histidine in the Pauly diazo reaction (test for unsubstituted imidazole) after treatment with H.[17] The reactions of histidine and imidazole with β-chloroethyl butyl and benzyl sulfides has been studied and the products isolated (see page 413).[17]

Among the groups occurring naturally with which H does not appear to react under physiological conditions of *p*H are the indole nitrogen of tryptophane,[9,17,58] the guanido group of arginine,[17,22] and the phenolic hydroxyl of tyrosine. Reaction with the phenolate ion, both of tyrosine[17] and of various phenols[48] has been noted, but at *p*H 7.35 the phenol group is largely undissociated.[2]

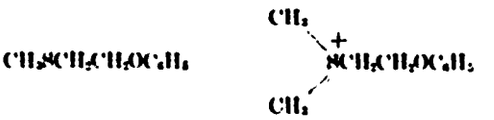
From the foregoing it can be seen that H, under physiological conditions of solvent, *p*H, and temperature, is capable of reacting with a wide variety of naturally occurring functional groups. The list of such groups in the case of H is qualitatively indistinguishable from that already presented on page 396 for the nitrogen mustards. Minor quantitative variations may be noted, however. Thus, at *p*H 7.35 the nitrogen mustards appear to react more readily with amino groups than does H. On the other hand, H appears to react more readily with carboxyl groups and with sulfides than do the nitrogen mustards. In this respect HN3 resembles H, however, more closely than it does HN1 or HN2.

As was noted for the nitrogen mustards, derivatives of H which might be formed *in vivo* are all stable compounds under conditions compatible with cell life. Direct evidence in support of this statement has been obtained whenever the stability of an H derivative has been investigated. In the case of those derivatives not specifically studied, stability may be inferred by analogy with other substances of similar structure.

There has been one hypothetical type of H derivative, however, concerning the stability of which there has been much speculation. As a working hypothesis it was suggested by Rydon[49,50] that H combines with proteins to form (2H protein) compounds of the following types, where Pr denotes protein:



Model experiments presented to support this hypothesis were also intended to show that the systemic effects of H "are due to its carriage in the body as the compound (2H protein) which releases H to react with sensitive body constituents, so producing the manifold toxic effects."[50] Subsequently it was noted that model compounds did not decompose in this manner.[17,50] Thus, on treatment of phenol with methyl β-chloroethyl sulfide (methyl-H), compound XXII is obtained which is stable to boiling strong alkali. On reaction with another alkylating agent, namely methyl iodide, the sulfonium salt XXIII results, which is unstable at alkaline *p*H values above 9.



(XXII) (XXIII)

A similar compound was obtained from phenol and butyl β-chloroethyl sulfide (butyl-H). On distillation with 2*N* NaOH, XXIII yielded phenol (85 per cent), XXII (9 per cent), dimethylsulfide (39 per cent), acetylene, and a small amount of methyl iodide. The butyl-H derivative decomposed similarly.

The Rydon theory has been appraised in this country,[24] and the following conclusions drawn: Since in the decomposition of XXIII only small amounts of methyl iodide and large amounts of phenol are formed, the major part of XXIII does not decompose according to Rydon's scheme,

$$2\text{H protein} \longrightarrow \text{H protein} + \text{H},$$

but decomposes in a different manner to yield products which do not possess alkylating properties. The above-described products of the decomposition of XXIII were isolated after distillation with 2*N* alkali, i.e., under experimental conditions known to decompose sulfonium bases with the formation of dialkyl sulfides and unsaturated hydrocarbons. This decomposition is fundamentally different from the one originally proposed by Rydon for 2H proteins. It was concluded, furthermore, that the experimental evidence for the existence of 2H protein compounds *in vivo* or *in vitro* is lacking, and that these hypothetical compounds do not explain the observed physiological behavior of H better than do the known chemical characteristics of H itself.

19.3.3 Reactions of β-Chloroethyl β-Hydroxyethyl Sulfide (ClH)

The fact already discussed (page 398), that ClH is an intermediate in the hydrolysis of H, made the examination of its alkylating properties of some interest. In all cases in which they have been examined, the reactions of the β-chloroethyl group of ClH are similar to those of H.[14,39a,b,d,b] It has been established that ClH reacts with anions by replacement of the chlorine atom to yield compounds of the general structure $HOCH_2CH_2SCH_2CH_2R$. The kinetics of the reaction are similar to those of H; i.e., ClH reacts according to the competition factor mechanism.[34d] Moreover, as may be seen from Table 7, the competition factors of various substances for ClH do not differ widely from those determined for H.

TABLE 7. Competition factors of various substances for H and for ClH.[34d]

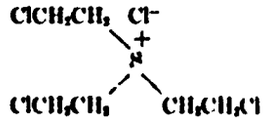
Substance	Competition factors H	ClH
Monothiophosphate	3.8×10^4	4.2×10^4
Thiosulfate	2.7×10^4	2.7×10^4
Cysteine	1.2×10^4	0.9×10^4
Thiocyanate	6.7×10^3	7.8×10^3
Chloride	2.1×10^2	2.4×10^2
Acetate	10	5.2

It has been shown that ClH reacts with the amino group of amino acids and peptides,[14] with the sulfur of TG;[14,39b] and methionine,[14] with the imidazole group of histidine,[14] with the pyridine nitrogen of pyridine and nicotinamide,[14] and with the carboxyl groups of sodium acetate[14,34d] and sodium hippurate.[14] Monoacetylthiodiglycol has been synthesized.[17] The products of the reaction of ClH with cysteine and with valine have been prepared.[1,39c] In the former case, reaction involved the sulfhydryl group, whereas with valine, alkylation of the amino group occurred. The isolation of a ClH glycine compound was mentioned on page 404.

19.3.4 Chemical Reactions of Sulfonium Salts Related to H

In Section 19.3.1 it was shown that, on hydrolysis with moderate quantities of water, H gives rise to several different sulfonium salts. The interesting chemical and toxicological properties of these sulfonium derivatives prompted an investigation of the properties of other sulfonium compounds of this type.

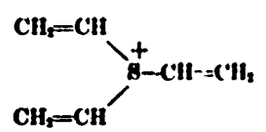
Compound XXIV, *tris*(β-chloroethyl)sulfonium chloride, was prepared by treatment of the corresponding hydroxyethyl derivative with thionyl chloride.[16]



(XXIV)

Compound XXIV and its transformation product, *bis*(β-chloroethyl)vinyl sulfonium chloride appear to be the only compounds known in which the sulfur of H is alkylated. In fact, there are several reports in the literature which attest to the resistance to alkylation of the sulfur of β-chloroethyl sulfides.[7,40,74]

When dissolved in water, XXIV liberates 3 equiv of HCl to form the trivinylsulfonium ion XXV, which has been isolated from the reaction mixture as a pierylsulfonate.[16]



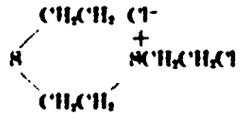
(XXV)

The HCl elimination is stepwise, the intermediate *bis*(β-chloroethyl)vinyl sulfonium compound having also been isolated. The rate of the HCl elimination is very sensitive to *p*H, being increased as the *p*H is raised. At *p*H 3.0 for example, the half-life time for the liberation of 2 equiv of HCl is about 25 minutes, and the third equivalent of HCl is not liberated. At *p*H 9, on the other hand, 3 equiv of HCl are produced in 10 minutes. Moreover, at *p*H 7.5, the rate of HCl formation is markedly dependent upon the nature and concentration of other substances in solution. Thus, an equivalent of borate or bicarbonate depresses the rate of HCl liberation almost 100-fold, whereas acetate and sulfate depress the rate slightly. This effect appears to be related to the extent of the dissociation of the salts in question at *p*H 7.5.[16]

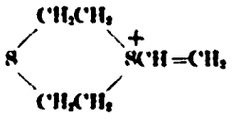
It may be noted that XXIV reacts readily with thiosulfate, as does the trivinyl derivative XXV.[40] Compound XXIV also reacts with cysteine and with pyridine.[16] In the former case, 3 equiv of sulfhydryl groups disappear, but *bis*(cysteinylethyl) sulfide is formed. With 2 equiv of cysteine the sulfide is not obtained. Similarly, in the case of pyridine, *bis*(β-pyridiniumethyl) sulfide is formed. It would appear,

therefore, that substitution of the 3 chlorine atoms of XXIV by cysteine or pyridine leads to the formation of an unstable sulfonium salt which decomposes to yield the sulfide.[16] However, when treated with alcoholic NaOH, XXIV yields *tris*(β-ethoxyethyl)-sulfonium chloride.[16]

β-Chloroethyl-1,4-dithiane sulfonium chloride (XXVI) was prepared by chlorination of the corresponding hydroxyethyl compound with thionyl chloride.[16]



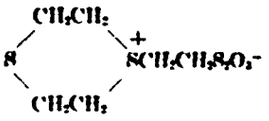
(XXVI)



(XXVII)

The behavior of XXVI in aqueous solution is in many respects similar to that of XXIV.[16] Thus, XXVI liberates HCl to form the vinyl compound XXVII which has been isolated as its picrylsulfonate. As was noted in the case of XXIV, the elimination of HCl from XXVI is sensitive to *p*H and is depressed by the presence of bicarbonate.[16]

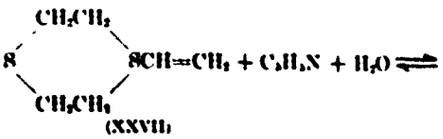
Both XXVI and XXVII react with thiosulfate to form the inner salt XXVIII:



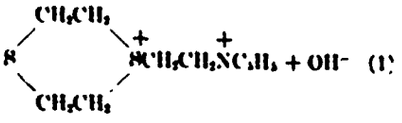
(XXVIII)

Evidence has been obtained which proves that the first step in this and all other alkylating reactions of XXVI is elimination of HCl to form the vinyl compound XXVII.[16] At *p*H 7.5 the reaction of XXVII with thiosulfate proceeds to completion.. At higher *p*H's, however, the reaction stops short of completion. Moreover, when the reaction product XXVIII is kept at alkaline *p*H values (8 9), it decomposes with the liberation of groups titratable with iodine.[16]

The β-chloroethyl and vinyl sulfonium salts XXVI and XXVII both react readily with pyridine to form the β-pyridinium ethyl-1,4-dithiane sulfonium salt XXIX, which has been obtained as the dichloride and the dipicrylsulfonate.[16] As may be seen in equation (1), the reaction is a reversible one. Proof for the reversibility of the reaction rests upon the following facts:[16]



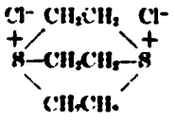
(XXVII)



(XXIX)

The forward reaction does not go to completion at *p*H 7.4, but rapidly attains an equilibrium condition. A study of the decomposition of the pyridinium compound XXIX revealed that the equilibrium attained by the forward and the reverse reactions was the same. Moreover, it can be seen that XXIX, in the course of its decomposition, should give rise to a vinyl group, and hence should act as an alkylating agent. Indeed, it was found that XXIX consumes thiosulfate and reacts with the amino group of alanine. In the reaction with thiosulfate, the inner salt XXVIII is formed. It should be noted that the behavior of these sulfonium salts is in many respects similar to that of sulfones (see page 412)

A third sulfonium salt of some interest, 8,8'-endoethylene-1,4-dithiane disulfonium dichloride (XXX) was formed by the reaction of TG with concentrated HCl at 100 C.[16]



(XXX)

The compound was obtained as a double salt with zinc chloride and as a dipicrylsulfonate. Upon treatment with silver carbonate XXX is transformed into the vinyl compound (XXVII).[16]

On the basis of the chemical data reviewed in this and a preceding section of this chapter, a correlation has been made between the chemical reactivity and the toxicity of a group of sulfonium salts.[16] It has been concluded that the more innocuous sulfonium salts all possess a relatively stable sulfonium sulfur atom, and do not possess any reactive alkylating side chains. The more toxic sulfonium salts, on the other hand, each contain either a reactive side chain, or a relatively unstable sulfonium sulfur atom, or both.[16]

19.4 CHEMICAL REACTIONS OF H SULFONE, DIVINYL SULFONE, H SULFOXIDE AND DIVINYL SULFOXIDE

The chemistry of the oxidation products of H has been studied very extensively. The interest in H sulfoxide and H sulfone, and their transformation products divinyl sulfoxide and divinyl sulfone, has been manifest for the most part in an endeavor to shed some light on the validity of the "sulfone theory." It will be recalled that, according to this theory, H must be oxidized in the skin to the sulfone, the latter being the vesicant agent. The sulfone theory was discussed previously (Section 19.3.2) and the reasons for its rejection were pointed out. Nevertheless, H sulfone (and the related compounds which are the subject of this section) has continued to receive much attention because of its vesicancy, toxicity, and close chemical relationship to H.

H sulfoxide is formed on oxidation of H with a variety of oxidizing agents,[28] such as H_2O_2 or nitric acid. Divinyl sulfoxide may be obtained in excellent yield by heating H sulfoxide with aqueous sodium carbonate for 1 hour.[21] H sulfone may be prepared, either from H or H sulfoxide, by oxidation with agents such as permanganate, chromic acid, or peracids. The conversion of H sulfone to divinyl sulfone may be accomplished with ease in a variety of ways.[15,28,50,53,59,70,73,75] On treatment of H sulfone with triethylamine in dry benzene, 2 moles of HCl are eliminated and divinyl sulfone is formed.[59] A similar reaction occurs when an aqueous solution of H sulfone is heated with calcium carbonate,[50] or when H sulfone is kept at room temperature in bicarbonate-buffered solution.[15,28,53]

The ease with which H sulfone eliminates HCl to form divinyl sulfone, coupled with the great chemical reactivity of the latter, has led to the now widely accepted view that H sulfone is relatively unreactive and must be transformed into divinyl sulfone prior to undergoing reaction.[15,28,49-51,53] Support for this contention derives from several considerations. To begin with, in every case where comparable data are available, H sulfone and divinyl sulfone yield the same reaction product with a given substance.[49] Even with proteins, it has been found that treatment with H sulfone and divinyl sulfone yields immunologically similar products.[50] The firmest support for the concept that H sulfone is transformed into divinyl sulfone prior to undergoing chemical reaction is derived from studies on reaction rates. It has been found that divinyl sulfone reacts with amino groups, thiosulfate, etc., more rapidly than does H sulfone,[15,53] and furthermore, that a bicarbonate-aged solution of H sulfone reacts with amino groups more rapidly than does a fresh solution of the sulfone.[53] The rate of the reactions of H sulfone with glycine or thiosulfate in aqueous solution is no greater than the rate of the elimination of HCl from the sulfone in the absence of these reactants.[15,53] In the case of thiosulfate, considerable amounts of HCl are formed in the early stages of the reaction before any disappearance of thiosulfate has taken place.[15]

19.4.1 Reactions of H Sulfone, Divinyl Sulfone, and H Sulfoxide with Water

H sulfone appears to be very stable in pure water.[28] Even on standing for many days, the *p*H of the solution is not very low, and silver nitrate gives a negative or faint positive test for Cl^-.[28] If the *p*H of an aqueous solution is raised, equivalent amounts of H^+ and Cl^- are liberated and divinyl sulfone is formed.[15,28,53] The elimination of HCl is catalyzed by OH^-, and depressed greatly in the presence of bicarbonate.[15] In water at *p*H 7.5 7.8 and 25 C, 1.06 equiv of HCl are formed within 3 minutes. In the presence of 1 equiv of $NaHCO_3$, only about 0.37 equiv of HCl is liberated within 30 minutes.[15] It has been noted that the elimination of HCl from H sulfone is slower in Ringer solution containing phosphate than in bicarbonate.[50] β-Chloroethylvinyl sulfone (prepared from H sulfone by treatment with 1 equiv of triethylamine in dry benzene) liberated HCl in Ringer phosphate more slowly than did H sulfone.[59]

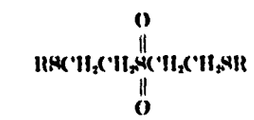
Divinyl sulfone appears to be relatively stable in aqueous solution. Since, as will be shown later, divinyl sulfone reacts readily with thiosulfate, the disappearance of reactive vinyl groups on aging the sulfone in aqueous bicarbonate (*p*H 8.4) was followed by determining the decrease in thiosulfate titer.[15] By this means, a disappearance of about 60 per cent of the divinyl sulfone in 94 hours was noted.[15] Addition of water to divinyl sulfone is reported to yield thioxane sulfone, presumably through thiodiglycol sulfone.[28]

In marked contrast to H sulfone, H sulfoxide liberates HCl only very slowly at physiological *p*H values.[15,28,50] The rate of HCl production is increased as the *p*H is raised, and is depressed in the presence of bicarbonate.[15] When heated with aqueous NaOH,

H sulfoxide gives rise to thioxane sulfoxide. The tendency for ring closure to occur is much less with the sulfoxide than with the sulfone, so that on heating with aqueous Na_2CO_3, divinyl sulfoxide is formed.[21]

19.1.2 Reactions of H Sulfone, Divinyl Sulfone, H Sulfoxide, and Divinyl Sulfoxide with Sulfhydryl Groups

It has been known for many years that H sulfone reacts readily with sulfhydryl compounds in general. With sodium thiophenates and mercaptides (i.e., the sulfhydryl compounds in alcoholic NaOH) at 100°C, compounds of the general structure

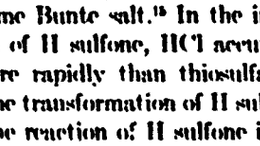


are formed.[59,68] Analogous reactions occur with sodium phenates and alcoholates.[59,68] Divinyl sulfone under similar conditions reacts in the same manner to form the same products.

Both H sulfone and divinyl sulfone react readily with thiosulfate in aqueous solution at *p*H 7.5 to form the same Bunte salt.[15] In the initial stages of the reaction of H sulfone, HCl accumulates in the solution more rapidly than thiosulfate disappears, indicating the transformation of H sulfone to divinyl sulfone.[15] The reaction of H sulfone is markedly inhibited by bicarbonate, whereas the reaction of divinyl sulfone is not, a clear indication that bicarbonate decreases the rate at which vinyl groups are formed but does not alter the reactivity of the vinyl groups once they are present.[15] The Bunte salt formed in the reaction with thiosulfate is unstable in alkaline solution. When kept at *p*H 8.7 for 24–48 hours, there is a liberation of groups (thiosulfate) which consume iodine.[15]

It has been found that the reaction of divinyl sulfone with sulfhydryl groups is very sensitive to slight changes in *p*H.[15,50] For example, the reactions with thiophenol to form *bis*(phenylthioethyl) sulfone is catalyzed by nitrogenous bases or bicarbonate.[15,50] In aqueous solution the rate of the reaction of divinyl sulfone with the sulfhydryl groups of cysteine or β-mercaptoethanol increases rapidly as the *p*H rises.[15] With cysteine, *bis*(cysteinylethyl) sulfone is formed.[15,50] This compound is so insoluble that it separates almost quantitatively from solution, and hence the reaction with cysteine has been suggested as a quantitative tool for the determination and characterization of divinyl sulfone.[50] It should be noted that, on treatment of *bis*(cysteinylethyl) sulfone with silver or mercury salts at moderately alkaline *p*H values, the sulfhydryl groups of cysteine are regenerated, as is divinyl sulfone.[50,53] With β-mercaptoethanol, divinyl sulfone yields *bis*[β-(β-hydroxyethylthio)ethyl]sulfone.[15] In contrast to the Bunte salt of divinyl sulfone, this product does not liberate reducing substances at *p*H 8.5.[15]

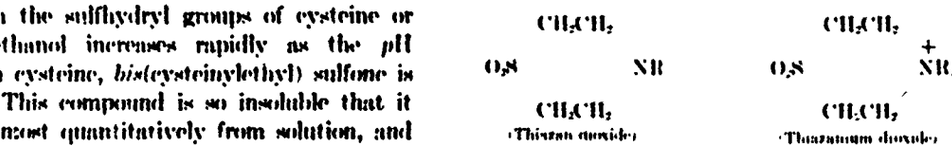
The reaction of H sulfoxide with sulfhydryl groups has not been studied extensively. With sodium thiophenates in alcohol, products of the structure



are formed.[68] With sodium phenates, condensation does not take place.[68] It has been found that divinyl sulfoxide reacts with sulfhydryl groups to yield compounds of the same general structure.[15,21] In all cases the reactions appear to be more sluggish than are the corresponding reactions of divinyl sulfone. The reaction of the sulfoxide with thiophenol, which was first reported not to occur,[59] requires the presence of catalytic quantities of a base.[21] Reactions with o-thiolbenzoic acid and cysteine have also been observed.[21] The rates of the reactions of divinyl sulfoxide with thiosulfate, cysteine, and β-mercaptoethanol in aqueous solution have been studied.[15] As was found to be the case with the sulfone, the rates are markedly sensitive to *p*H, increasing as the *p*H rises. The reactions of the sulfoxide, however, are much slower than are those of the sulfone.[15]

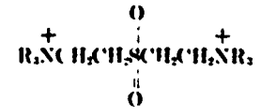
19.1.3 Reactions of H Sulfone, Divinyl Sulfone, H Sulfoxide, and Divinyl Sulfoxide with Nitrogenous Bases

The reactions of H sulfone and divinyl sulfone with numerous nitrogenous bases have been studied extensively and under a variety of conditions. The early work revealed that, with primary and secondary amines, cyclic thiazan and thiazanium dioxide derivatives are usually obtained,[59,68,71] such as:

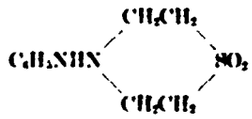


(Thiazan dioxide) (Thiazanium dioxide)

With tertiary amines, on the other hand, disubstituted quaternary derivatives result.[71]

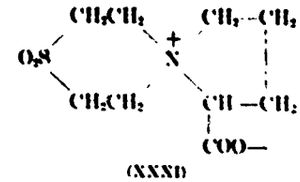


The investigations which established these general rules are in the open literature. For the most part the reactions involved substances (primary and secondary aliphatic and aromatic amines) of little physiological interest, and were performed under drastic experimental conditions, the base and the sulfone being heated in aqueous or alcoholic alkali. However, with one exception, the general rules thus elucidated have been fully confirmed by the more recent work. It has been found that aniline gives both the open chain and cyclic products.[49] Prior to World War II it had also been established[59] that the sulfones reacted with phenylhydrazine to yield



and that no reaction occurred with acid chlorides, ammonia, hydrazine, phthalimide, benzaldehyde, or formic acid.[59]

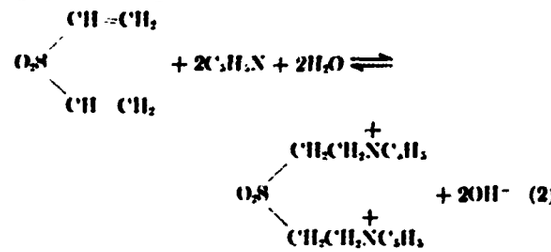
There were also indications in the open literature that the sulfones reacted with the amino groups of amino acids. With glycine ester in alcoholic Na_2CO_3, ethyl-1,4-thiazan-4-acetate-1-dioxide, or 1,4-thiazan-4-acetic acid-1-dioxide had been obtained.[59,60] On heating glycine or phenylalanine in aqueous Na_2CO_3, 1,4-thiazan-4-acetic acid-1-dioxide and the corresponding phenylpropionic acid derivative resulted.[71] More recently, however, it was shown that both II sulfone and divinyl sulfone reacted rapidly and completely at 30–37°C with the amino groups of amino acids in aqueous bicarbonate solution.[52] The products of the reaction with glycine, alanine, phenylalanine, and tyrosine were prepared and found to be substituted thiazan dioxides.[52] Identical products were obtained from II sulfone and divinyl sulfone.[52] Moreover, the same derivatives resulted no matter which of the three methods of preparation outlined above were employed.[52] Rate studies indicated that divinyl sulfone combined with the amino groups of amino acids more rapidly than did II sulfone.[52] In the case of the latter, the combination with amino groups did not proceed faster in the presence of amino acids than did the elimination of HCl in the absence of amino acids.[52] With proline, the betaine (XXXI) was obtained.[15,50]



(XXXI)

Reaction of divinyl sulfone with the following compounds has also been noted:[49,50] anthranilic acid, N-methylanthranilic acid, creatine, piperidine, glycylglycine, N-methylsulfanilic acid, and taurine. No reaction between divinyl sulfone and the following compounds took place:[50] glucosamine or its hydrochloride, maleic anhydride, N,N-dimethylanthranilic acid, methyl-N,N-dimethylanthranilate·HCl, and N,N-dimethylsulfanilic acid.

The reaction of divinyl sulfone with certain tertiary bases has been studied in some detail.[15] With pyridine, *bis*(β-pyridiniumethyl) sulfone dichloride is formed.[15,71] In water at *p*H 7.5, the reaction to form the pyridinium derivative proceeds rapidly, but does not reach completion, an equilibrium condition being attained.[15] The reverse reaction, the decomposition of the pyridinium derivative was also investigated and found to reach the same equilibrium value, thus proving the reversibility of the reaction [equation (2)].[15]



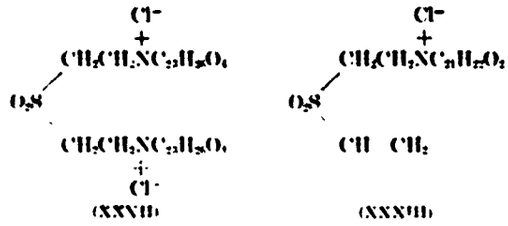
(2)

The pyridinium derivative was synthesized by reacting a mixture of pyridine and pyridine hydrochloride with divinyl sulfone in alcoholic solution at room temperature.[15] It was found, as was to be anticipated from equation (2), that the position of the equilibrium is determined by the *p*H of the solution. High *p*H values favor the reverse reaction, whereas lower *p*H values favor the forward reactions.[15] From equation (2) it may be predicted that in aqueous solution *bis*(β-pyridiniumethyl) sulfone should give rise to reactive vinyl groups. As was expected, reaction with the sulfhydryl group of cysteine, the amino group of alanine, and with thiosulfate was

noted.[15] With cysteine, *bis*(cysteinylethyl) sulfone was formed.[15] For purposes of comparison it may be noted that *bis*(β-pyridiniumethyl) sulfide is stable under these conditions, no reaction with cysteine occurring in 48 hours.[15]

An equilibrium reaction analogous to that observed with pyridine was also found to occur between divinyl sulfone and nicotinic acid or nicotinamide. With the latter two compounds, however, the equilibrium was further toward the left [equation (2)] than was found to be the case with pyridine.[15]

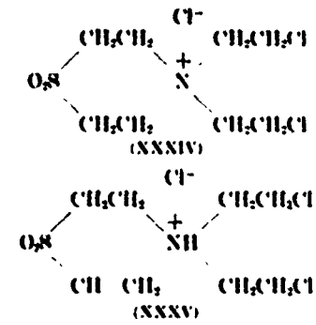
Attempts have been made to prepare the products of the reaction of divinyl sulfone with the following bases:[15] ethyl-*bis*(β-chloroethyl)amine, methyl-*bis*(β-chloroethyl)amine, *tris*(β-chloroethyl)amine, ethyldiethanolamine, methyldiethanolamine, diethanolamine, quinoline, nicotine, brucine, and strychnine. The experimental conditions employed were the same as those employed in the synthesis of the pyridine derivative. With the β-chloroethylamines, ethyldiethanolamine, methyldiethanolamine, quinoline, and nicotine, reaction products were not obtained.[15] With brucine, a derivative of the structure XXXII was obtained, and strychnine yielded XXXIII.[15]



(XXXII) (XXXIII)

Both of these compounds consume thiosulfate when kept in aqueous solution.[15] In the case of XXXII the consumption of thiosulfate must be attributed to decomposition of the compound with the liberation of alkylating groups. Compound XXXIII, however, still retains one vinyl group which might react with thiosulfate.

Divinyl sulfone reacts with diethanolamine hydrochloride in alcohol to yield *bis*(β-hydroxyethyl)-1,4-thiazanium dioxide chloride.[15] This substance slowly liberates alkylating groups when kept in aqueous solution at *p*H 7.5 in the presence of cysteine or thiosulfate.[15] With cysteine the dicysteinyl derivative of divinyl sultone is formed. When treated with thionyl chloride, the hydroxyethyl compound is chlorinated to yield either XXXIV or the isomeric XXXV.[15] There is some evidence to indicate that XXXV exists in aqueous solution. Compound XXXV is both a monosubstituted derivative of divinyl sulfone and a nitrogen mustard, and, therefore, exhibits some of the properties of both classes of compounds.[15]

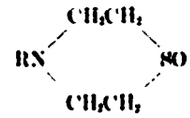


(XXXIV) (XXXV)

In aqueous solution the β-chloroethyl groups hydrolyze with the intermediate formation of ethylenimonium rings.[15] Even after hydrolysis of the chloroethyl group, however, the substance reacts with cysteine, indicating the presence of a reactive vinyl group. The chlorinated product reacts readily with thiosulfate, consuming 3 equiv in 24 hours.[15]

The fact that divinyl sulfone reacts with proline to give the betaine XXXI has been mentioned before. It has been noted that this substance is unstable at *p*H 7.4.[15] It consumes thiosulfate and reacts with the sulfhydryl group of cysteine to form the dicysteinyl derivative of divinyl sulfone.

The reaction between H sulfoxide and nitrogenous bases has not been studied in great detail. In alcoholic sodium carbonate solution, primary aliphatic amines (methyl, ethyl, butyl, benzylamine, etc.) yield the substituted thiazan oxides.[71]



Secondary alkyl amines, on the other hand form open chain compounds of the general structure:[71]

With a tertiary amine, trimethylamine, *bis*(trimethylammoniumethyl) sulfoxide dichloride, results.[71]

Divinyl sulfoxide, like divinyl sulfone, reacts with pyridine in aqueous solution, although the rate and extent of the reaction is much less than was that of the sulfone.[15] As was observed with the sulfone, the reaction of the sulfoxide with pyridine appears to be a reversible one, the position of the equilibrium being determined by the *p*H of the medium.[15] With methyl-

amine divinyl sulfoxide yields N-methylthiazan oxide.[31]

19.4.4 Discussion

The information summarized in this and the previous Section (19.3) indicates a striking similarity in behavior between β-substituted sulfones and β-substituted sulfonium salts.[16] These similarities may be summarized as follows:[16] The β-chloroethyl sulfones and sultonium salts lose HCl by elimination with the formation of reactive vinyl groups. The elimination reaction in each case is similarly influenced by changes in *p*H and by the presence of salts (bicarbonate). The sulfonium salts and H sulfone appear to react readily with a number of substances to form β-substituted derivatives. In each case, however, chemical reaction is preceded by the elimination of HCl and the formation of reactive vinyl groups. There is, in addition, a striking similarity in the behavior of the vinyl sulfonium and vinyl sulfone groups thus formed. Both groups react readily with pyridine in aqueous solution at *p*H 7.5 to form β-pyridinium derivatives. In both cases the reaction is reversible, and the speed of attainment of equilibrium, as well as the position of the equilibrium, is similarly influenced by *p*H. Furthermore, the pyridinium derivatives in both cases are unstable, and decompose with the formation of reactive alkylating groups which combine readily with sulfhydryl groups, amino groups, etc. Vinyl sulfonium and vinyl sulfone groups react similarly with thiosulfate. In both cases the rate of reaction increases with rising *p*H and is unaffected by bicarbonate. At *p*H 8.5 9.5, however, both thiosulfate derivatives decompose with the liberation of substances titratable with iodine.

Finally, it has been noted that acetic acid is eliminated from diacetylthiodiglycol methylsulfonium picrylsulfonate and also from diacetylthiodiglycol sulfone by treatment with aqueous bicarbonate, and that, in both cases, the resulting products consume thiosulfate.[20]

For the general problem of vesication, it is of some interest that derivatives of divinyl sulfone and H sulfone are far more unstable than are similar derivatives of H. It is also of interest that some of the sulfone compounds decompose to yield reactive alkylating groups. It seems not unlikely, therefore, that *in vivo* the products of the reaction of divinyl sulfone with cellular constituents would undergo a similar decomposition.[15] Should such a decomposition occur, it would become possible for 1 molecule of sulfone to react in succession with several functional groups in a cell until it finally either reacted with some tissue component with which it formed a stable compound or was removed by the circulation.[15]

19.5 CHEMICAL REACTIONS OF ALKYL AND ARYL β CHLOROETHYL SULFIDES

In the course of the work on vesicants, the chemistry of several substances of the general formula $RSCH_2CH_2Cl$ (R = alkyl, phenyl, or benzyl group) has been investigated. Interest in these so-called one-handed mustards has been stimulated by two considerations. In the first place, the chemistry of these substances has been investigated in order to ascertain, if possible, whether their poor vesicant power relative to H is associated with differences in chemical reactivity.[34a] In the second place, studies on one-handed vesicants were undertaken in the belief that they would lead to chemistry of greater simplicity and equal significance to that which could be derived from a study of H itself.[17]

It has been found that the one-handed vesicants hydrolyze at a unimolecular rate as was observed for H.[34a] The absolute value of the hydrolysis rate is different for each compound and depends upon the nature of the R group. Thus, the hydrolysis rates in descending order are: ethyl β-chloroethyl sulfide (ethyl-H), propyl β-chloroethyl sulfide (propyl-H), H, phenyl β-chloroethyl sulfide (phenyl-H).[34a]

It has been found that the substances listed above behave like H in reactions involving the β-chloroethyl group, substitution of the chlorine occurring by a unimolecular process according to the competition factor principle.[34a] Moreover, the competition factors for ethyl-H, propyl-H, phenyl-H, and H are the same for a given ion, e.g., acetate, chloride, thiocyanate, thiosulfate, and monothiophosphate.[34a] Since the competition factors refer to hydrolysis rates in water as a reference, the relative rates of reaction of the four vesicants listed with all of the above anions is the same compared to their rates of reaction with water. The absolute reaction rates with anions varies with the vesicant in the same order as the hydrolysis rates with water given above, i.e., ethyl-H > propyl-H > H > phenyl-H.[34a] The intermediate position of the highly vesicant H in this list of otherwise relatively poor vesicants, indicates that there is as yet no satisfactory chemical basis to explain the considerable differences in physiological potency which exist between H and the one-handed vesicants (see Chapters 5 and 23).

The reactions of butyl β-chloroethyl sulfide (butyl-

II) and benzyl β-chloroethyl sulfide (benzyl-II) with amino acids have been studied in some detail.[17] With cysteine in alkaline solution benzyl-II yields S-benzylthioethylcysteine, whereas with the monoamino, monocarboxylic amino acids reaction occurs on the amino group with the formation of mono- or disubstituted benzyl-II derivatives of the general formulas[17]

$$C_6H_5CH_2SCH_2CH_2NHR$$

or

$$(C_6H_5CH_2SCH_2CH_2)_2NR$$

Monosubstituted derivatives have been obtained with alanine, valine, isoleucine, and phenylalanine.[17] Disubstituted derivatives have been obtained with tryptophane, although the indole nitrogen does not appear to react.[17] A mixture of mono- and disubstituted derivatives resulted from the reaction of benzyl-II with glycine, leucine, and tyrosine.[17] In the case of tyrosine, reaction occurs at both the amino and the phenolic hydroxyl group. It has been noted that the monosubstituted derivatives are stable to boiling in an HCl-formic acid mixture of the type sometimes employed to hydrolyze proteins.[17] The disubstituted tyrosine and tryptophane derivatives are stable in alkali on prolonged standing at room temperature or on short heating to 100°C.[17]

Butyl-II gives the same types of derivatives with the monoamino acids as does benzyl-II. With lysine, the ε-butylthioethyl derivative has been obtained by heating the copper salt of lysine with butyl-II in alkaline solution. The reaction of butyl-II with the imidazole group has been studied in some detail.[17] With imidazole and 6 moles of vesicant, disubstitution occurs with the formation of a quaternary salt. A monosubstituted derivative of imidazole has also been obtained. With histidine in the presence of excess butyl-II, a trisubstitution product containing one quaternary nitrogen atom is formed.[17] Apparently two butyl-II residues have reacted with the imidazole group and one with the α-amino group, since benzoylhistidine yields a disubstitution product. With glycyltryptophane there is evidence to indicate that butyl-II combines with the carboxyl group to form an ester.[17]

19.6 CHEMICAL REACTIONS OF 1,2-*bis*-(β-CHLOROETHYLTHIO)ETHANE (Q) AND *bis*(β-CHLOROETHYLTHIOETHYL) ETHER (T)

19.6.1 Transformations of 1,2-*bis*-(β-Chloroethylthio)ethane (Q) in Water

The kinetics of the hydrolysis of Q in dilute solution are reported in Chapter 20. Under these conditions complete hydrolysis to Q glycol occurs (Figure 3). When the ratio of water to Q is reduced to 50 volumes, the hydrolysis of Q is slow, due to its extremely low rate of dissolution, and after 2–3 days' shaking, when 2 equiv of Cl^- have been liberated, only about 80–85 per cent of the H^+ to be expected on complete hydrolysis of Q has been formed. This finding indicates that sulfonium salts are present in the hydrolysate.[12,19] The fact that the liberation of H^+ continues after the liberation of Cl^- is complete makes it probable that some of the sulfonium salts formed during the hydrolysis of Q are unstable.[12] If aqueous bicarbonate is substituted for water, the hydrolysis appears to be somewhat slower, and the extent of sulfonium salt formation is less.[12]

After hydrolysis of Q with either water or aqueous bicarbonate, a precipitate is present in the reaction mixture.[12] The insoluble product, obtained in 35 per cent yield, was shown to be a higher homolog of Q glycol, pentaethylenetetrasulfide-ω,ω′-diol (XXXI).[12] The same compound was prepared by reaction of Q with 2 equiv of β-mercaptoethanol, and the identity of the isolated product and the synthesized compound was established by comparison of the melting points of the diacetyl and dibenzoyl derivatives.[12] The formation of pentaethylenetetrasulfide-ω,ω′-diol was presumed to occur according to the reaction sequence given in Figure 3. According to this scheme the diol would be formed by hydrolytic cleavage of the sulfonium salt of Q chlorohydrin with Q glycol

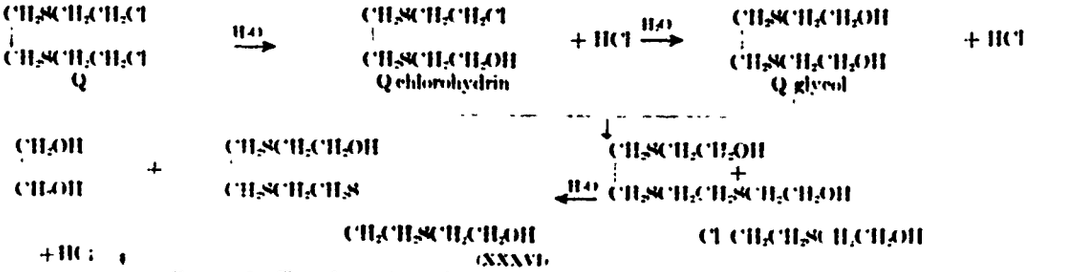


FIGURE 3. Transformations of 1,2-*bis*(β-chloroethylthio)ethane (Q) in water.

to break the carbon-sulfur bond to the β-hydroxyethyl group. Either of the other two carbon-sulfur bonds to the sulfonium group might break, and there are several other sulfonium salts possible which could undergo similar cleavage. In either case higher or lower homologs of the diol isolated would result.[12,19] Actually, the diol isolated melted about 6 8 C low, indicating contamination with other substances, probably homologs. Q glycol was also isolated from the hydrolysate in 20 25 per cent yield.[12]

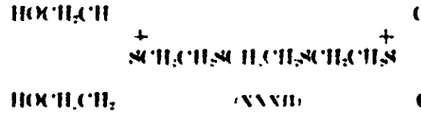
19.6.2 Reactions of β-Chloroethyl Groups of Q with Compounds of Biochemical Interest

The reactions of Q with a variety of functional groups was investigated [12] in much the same manner as was done in the case of the nitrogen mustards. In aqueous bicarbonate at 25 C it was found that Q combines with the amino groups of numerous amino acids,[12] namely, glycine, alanine, histidine, arginine, lysine, glutamic acid, serine, phenylalanine, methionine, and the peptide glycylglycine. The extent of the reaction was increased by raising the *p*H. Evidence was obtained for a reaction of Q with the sulfide group of methionine.[12]

By the use of a competition method, employing glycine as a reference compound (see page 403), it was noted that Q combines readily with imidazole, the pyridine nitrogen of pyridine itself, nicotinic acid and nicotinamide, the imino nitrogen of proline, the carboxyl group of sodium acetate and carbobenzoxy glutamic acid, the phosphate group of Na_2HPO_4 or sodium glycerophosphate, and the sulfide sulfur of thiodiglycol (TG).[12] Q shows somewhat less activity toward the tertiary nitrogen of aliphatic amines such as triethylamine or triethanolamine.[12] Employing thiosulfate as the reference substance, it was found that Q combines with hexamethylene tetramine.[12]

Q reacts readily with sulfhydryl groups, as exemplified by cysteine or thiosulfate.[12] The products of these reactions, the dicysteinyl derivative and the Bunte salt of Q have been isolated.[12] The kinetics of the thiosulfate reaction have been studied, and it has been noted that the process, as was the case with H, is first order and independent of thiosulfate concentration.[19]

The product of the reaction of Q with thiodiglycol



(XXXII)

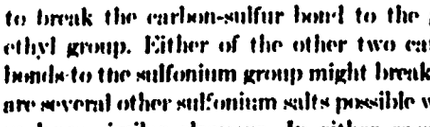
has been isolated as a picrylsulfonate and found to have the structure XXXII.[12]

The hydrolysis of XXXII has been investigated in 50 per cent acetone and found to be considerably faster than that of the analogous compound from H and TG.[12] Compound XXXII also reacts with thiosulfate, and once again the reactivity is greater than that of the analogous H compound.[12] In fact, it has been pointed out that the sulfonium salts of H, Q, and *bis*(β-chloroethylthioethyl) ether (T) with 2 equiv of TG parallel in their rates of hydrolysis and reactivity toward thiosulfate, the reactivity of the parent vesicants.[18,19] Thus, for both the chloro and the sulfonium compounds the reactivity in descending order is Q>T>H.[18,19] Furthermore, the vesicancy and toxicity of the chloro compounds are in the same order.

As a result of these studies, it would appear that *in vivo* Q would react with the same types of functional groups as would H or the nitrogen mustards. Q differs from H, however, in the stability of its oxidation products. Both the sulfoxides and the disulfone of Q are remarkably resistant to hydrolysis either in water or in aqueous bicarbonate.[19] A negative test for Cl^- was obtained even after Q disulfone had remained for 25 days in aqueous bicarbonate solution.[19]

19.6.3 Transformations of *bis*(β-Chloroethylthioethyl) Ether (T) in Water

The kinetics of the hydrolysis of T in dilute solution have been investigated in some detail (see Chapter 20). In more concentrated solutions (i.e., 1 per cent suspensions) T is reported to yield a mixture of oily sulfonium salts which had a half-life time of hydrolysis estimated to be 3-4 days.[18] Since T and its hydrolysis products each contain two sulfur atoms, the possibilities are great for the formation of several different sulfonium salts. By treatment of T with an aqueous solution of TG, the sulfonium salt (XXXIII) was obtained as a Reinecke salt.[18] The substance hydrolyzed slowly, 75 per cent in 8 days, and consumed thiosulfate (see Section 19.6.2).[19]



(XXXIII)

The reactions of the β-chloroethyl groups of T with compounds of biochemical interest appear not to have been investigated. The reactions may be expected to parallel those of H and Q.

Chapter 20

KINETICS OF REACTIONS OF SULFUR AND NITROGEN MUSTARDS

By *Barnett Cohen*

20.1 INTRODUCTION

THE KINETICS of the reactions of the sulfur and nitrogen mustards, as revealed by investigations conducted in the United States and United Kingdom during World War II, are summarized in this chapter.* Although the data are reviewed here because of their significance to physiological mechanisms of action, it should be noted that they bear also upon the contamination and decontamination of water, food supplies, matériel, and terrain, and upon the stabilization of the agents in storage.

The kinetic data may be reconciled with the following two-step mechanism for the reactions of both the sulfur and nitrogen mustards. $RZCH_2CH_2Cl$ is taken as a model β-chloroethyl compound in which Z represents the sulfur or nitrogen atom:

Step A. The reversible thermal activation to a cyclic onium cation with liberation of Cl^-:

$$RZCH_2CH_2Cl \rightleftharpoons RZ^+CH_2CH_2 + Cl^- \qquad (1)$$

Step B. The reaction of the cyclic onium cation with anions and with various uncharged nucleophilic molecules to form the end products of the overall reaction:

$$RZ^+CH_2CH_2 + X^- \longrightarrow RZCH_2CH_2X \qquad (2a)$$

$$RZ^+CH_2CH_2 + HX \longrightarrow RZCH_2CH_2X + H^+ \qquad (2b)$$

$$RZ^+CH_2CH_2 + RX \longrightarrow RZCH_2CH_2X^+R \qquad (2c)$$

Representative examples of X^- in equation (2a) are Cl^- (in which case step B is the reversal of step A), OH^-, $RCOO^-$, RS^-, and $S_2O_3^{--}$. Important examples of HX in equation (2b) are H_2O and RNH_2. Important examples of RX in equation (2c) are reactions with tertiary amines (e.g., pyridine) and alkyl sulfides (e.g., methionine). H^+ is liberated only in the case of the second of the three possible types of reaction in step B.

The hydrolysis products of sulfur mustards (e.g., thiodiglycol) can enter reaction (2c) with the formation of a series of sulfonium derivatives. Linear and cyclic quaternary ammonium derivatives can be formed by comparable reactions of the hydrolysis products of the nitrogen mustards. Moreover, the cyclic onium cation can react with the tertiary nitrogen atom of an unchanged nitrogen mustard to form a series of linear and cyclic polymers containing β-chloroethyl groups. These latter reactions are quantitatively important in concentrated solutions.

In the cases of the important nitrogen and sulfur mustards, which contain more than one β-chloroethyl group, the two-step reaction is repeated with each group.

Step A is the rate-determining reaction of the sulfur mustards. In the case of the nitrogen mustards, owing to the greater basicity of nitrogen relative to sulfur, step B is so much slower that it becomes the rate-controlling reaction. This is the basis for important quantitative differences between the reaction kinetics of the two classes of compounds. The cyclic onium cations of the nitrogen mustards accumulate in solution and then disappear as a result of hydrolysis and other reactions: the rate of disappearance of the onium cation varies with the nature and concentration of X^-, HX, and RX. In contrast, the cyclic sulfonium cation of the sulfur mustards does not accumulate to an appreciable extent, but the rate of formation of the final products is still dependent on the nature and concentration of X^-, HX, and RX. In the case of the sulfur mustards it has not been possible to determine the absolute rates of individual reactions in step B, but the relative rates of the reaction of the cyclic onium ion with pairs of "competitors" (X^-, HX, RX) can be ascertained experimentally. In this manner a series of relative velocity constants or competition factors has been built up. In view of the important physiological roles attributed to thiol compounds in metabolism, it is of interest to note that thiol anions (e.g., thiophosphonates, thiosulfate, cysteine) have uniquely high reaction rates with activated sulfur mustard.

The overall reaction rate in the case of the sulfur mustards is independent of *p*H over a wide range.

* Based on information available to Division 9 of the National Defense Research Committee as of September 1, 1945.

The corresponding reactions of the nitrogen mustards are *p*H-dependent. This results from the fact that the nitrogen mustards are weak bases which can undergo the initial reaction of cyclization (step A) only when they are in the form of the uncharged base molecule. Inasmuch as reaction (2b) (including hydrolysis) liberates H^+, the kinetics of the nitrogen mustards in unbuffered solutions may become highly complex.

In the detailed review which follows, the nitrogen mustards are considered first because the theory of their reaction mechanisms is based on more complete and direct evidence than is available for the sulfur compounds.

20.2 β-CHLOROETHYLAMINES IN HOMOGENEOUS SOLUTION

A tendency toward intramolecular cyclization as the initial reaction in a polar solvent is a characteristic property of primary, secondary, and tertiary alkylamines in which one or more alkyl groups are halogenated in the beta to omega position. The transformation yields halide, and a more or less stable heterocyclic compound. In the case of primary and secondary amines, the heterocycle may be either an imine or an immonium ion, depending upon the *p*H. Tertiary amines yield exclusively the immonium ion. The investigations of the past several years upon the tertiary β-chloroethylamines have considerably extended the description of the chemistry and kinetics of this interesting group of compounds,[2,5,7,9-11,15] and in particular have demonstrated the considerable reactivity of the cyclic ethylenimmonium ions as alkylating agents.

In the case of the *primary* halogenated alkylamines, the kinetics of the cyclization process in aqueous and part-aqueous solutions had been studied rather extensively before the war.[16] The forward process of ring formation, under proper conditions, was established as a strictly first-order reaction unaffected by moderate concentrations of salt, alkali, or the usual contaminants:

$$XCH_2(CH_2)_nNH_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH_2(CH_2)_nNH_2^+ + X^-$$

$$\Downarrow$$

$$CH_2(CH_2)_nNH + H^+$$

The rate of cyclization was shown to be influenced by the length of the side chain, by the substituents thereon, and by the nature of the halogen and of the solvent.[16] As indicated in the equation above, the process was known to be reversible, but the kinetics of the back reaction do not seem to have been studied in the early investigations, except for unsuccessful attempts[16] to determine the equilibrium constant in the β-chloroethylamine system. The failure was probably due to interference by side reactions (polymerizations).[16] It is, in fact, known that dimerization and polymerization can take place and become quantitatively important in concentrated solutions and at elevated temperatures.[12]

The nitrogen mustards which have been of greatest interest as potential chemical warfare agents during World War II are all tertiary amines of the general type $(ClCH_2CH_2)_2NR$ where R is either an alkyl or a β-chloroethyl group. Consequently the most detailed recent studies concern these tertiary amines, but primary and secondary halogenated alkylamines have also received some attention.

Since for halogenated alkylamines in general the process of cyclization consists in a displacement of the alkyl halogen by the basic nitrogen atom, the basicity of the nitrogen atom is a factor determining the ease of the displacement. Moreover, cyclization cannot occur when a proton becomes coordinated with the nitrogen atom. Consequently, in the case of the nitrogen mustards, which are all more or less weak bases, the reaction rate will be a function of *p*H in solutions of moderate and low *p*H. For the same reason, the salts of the nitrogen mustards, in the absence of sufficient excess of strong acid, suffer some dissociation to the free base which will cyclize at its characteristic rate. This accounts for the finding that their hydrochlorides in water solution hydrolyze, but only at a very slow rate. For example, it has been calculated that a 0.1*M* solution of the hydrochloride of methyl-*bis*(β-chloroethyl)amine (HN2), in the presence of a slight excess of HCl, decomposes at a unimolecular rate with a half life of approximately 3 years[43b] (dissociation of the base, cyclization, and subsequent hydrolysis were included in the estimate).

In a natural water containing a dissolved nitrogen mustard, or in an aged solution of a nitrogen mustard in distilled water, uncontrolled acidification occurs, usually as a result of the hydrolysis of the cyclic intermediate. The concentration of residual free amine is thus altered, thereby complicating the kinetics of the initial cyclization reaction and also of subsequent reactions. The result in such unbuffered

solutions is a complex shifting equilibrium of components and reactions which are extremely difficult to formulate. In such cases, the end products at equilibrium will depend more or less on the initial concentration of the amine, its solubility, and the reactivity of each component of the system as conditioned by the progressively changing *p*H during the reaction.

In kinetic studies the complications mentioned above have generally been avoided in part by measuring the reaction rate in the presence of excess alkali.[46] Procedures[3,4b] employing buffers to maintain constant *p*H have the disadvantage of introducing buffer anions which may modify the subsequent reactions of the cyclic imonium ion. A theoretically more satisfactory and flexible method[11] maintains constant *p*H without buffers by means of successive micro-additions of alkali under electrometric control. Under these conditions, the observed rate of cyclization is proportional to the degree of acid dissociation (α) of the ammonium ion of the amine, thus:

$$\text{Obs. rate constant, } k_1' = \alpha k_1 = \frac{K_a'}{K_a' + [H^+]} \cdot k_1$$

where k_1 is the rate constant at *p*H conditions under which the ammonium ion is fully dissociated ($\alpha = 1$), and K_a' is the apparent dissociation constant of the ammonium ion as an acid.

20.2.1 General Formulation of Reactions

The more or less systematic kinetic studies which are the main concern of this survey were conducted under three general types of experimental conditions: (1) in unbuffered water held at constant *p*H, with the amines at low (0.0005–0.05*M*) concentrations;[11,28] (2) in bicarbonate-buffered water (*p*H 7.5–8.5), usually with the amines at relatively high (0.03–0.15*M*) concentrations;[4,9] and (3) in unbuffered acetone-water solution, with the amines at relatively high concentrations.[2,7,10,45c] The data establish with high probability that the reactions of the tertiary β-chloroethylamines follow the general scheme outlined in the introduction (Section 20.1). For these compounds step A may be written with its velocity constants as:

$$R_2NCH_2CH_2Cl \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R_2\overset{+}{N}CH_2\overset{\cdots}{\underset{\cdots}{C}}H_2 + Cl^- \qquad (1a)$$

Under the experimental conditions the possible simultaneous and successive reactions in step B are:

$$R_2\overset{+}{N}CH_2\overset{\cdots}{\underset{\cdots}{C}}H_2 + H_2O \xrightarrow{k_2} R_2NCH_2CH_2OH + H^+ \qquad (2d)$$

$$R_2\overset{+}{N}CH_2\overset{\cdots}{\underset{\cdots}{C}}H_2 + R_2NCH_2CH_2Cl \xrightarrow{k_2} \text{linear and cyclic dimers} \qquad (2e)$$

$$R_2\overset{+}{N}CH_2\overset{\cdots}{\underset{\cdots}{C}}H_2 + R_2NCH_2CH_2OH \xrightarrow{k_2} \text{+ } R_2NCH_2CH_2\overset{+}{N}(R)_2CH_2CH_2OH \qquad (2f)$$

In the case of amines containing two or three β-chloroethyl groups, the reaction sequence is undergone by each such group in succession.

In the following presentation, cyclization (1a), reversal of cyclization (1a), hydrolysis [(2d), a special case of (2b)], dimerization [(2e), a special case of (2e)], and addition of electron donors [certain reactions of types (2a) and (2e), including (2f) as a special case] are discussed consecutively.

20.2.2 Cyclization

The observed rate of the forward reaction of the nitrogen mustards and their analogs in water at constant *p*H has been found to conform strictly to that of a first-order process in dilute (up to 0.01*M*) solutions of the amines, and to be complicated by higher order reactions at higher concentrations.[11] The average heat of activation of this reaction in dilute solution is approximately 22.5 kcal/mole for the two tertiary and the two secondary *mono*(β-chloroethyl)-amines examined, and 24.5 ± 1 kcal/mole for the seven tertiary *bis*(β-chloroethyl)amines (see Table 1).

Reaction (1a) can be conceived[32] as proceeding through an intermediate carbonium ion (Ia) stage:

$$\underset{(I)}{R_2NCH_2CH_2Cl} \rightleftharpoons \underset{(Ia)}{R_2\overset{+}{N}CH_2\overset{\cdots}{\underset{\cdots}{C}}H_2Cl} \rightleftharpoons \underset{(II)}{R_2\overset{+}{N}CH_2CH_2} + Cl^-$$

The hypothetical compound, Ia, should hydrolyze directly through an S_N1 process, and titrimetric evidence tending to support this mechanism has been offered.[4b] However, careful electrometric measurements failed to corroborate this observation.[11,28a] The postulated carbonium ion is doubtless formed, but its great ease of intramolecular cyclization through the influence of the electron donating central nitrogen atom should leave practically none of the ion available for the much slower bimolecular reaction with water.

In agreement with the evidence that the rate of cyclization is determined by the thermal activation of the uncharged amine, it was shown, in the case of

TABLE 1. Kinetics of initial cyclization of certain β-chloroethylamines. The compounds are arranged in the order of increasing stability in water at 25 C.

Compound	Activation energy in water (kcal/mole)	Conc. = 0.0005–0.0025 *M* in water[a]					Conc. = 0.005–0.15 *M* in 66.7 per cent acetone in water [a]	
		25 C		37 C			25 C	
		pK_a'	k_1 (min^{-1})	k_1 (min^{-1})	pH = 7.4		Relative[a] pK_a'	k_1 (min^{-1})
					α	$t_{\frac{1}{2}}$ (min)		
$N(CH_2CH_2Cl)_2(CH(CH_3)_2)$	23.0	6.7	1.86	8.20	0.80	0.004	..	...
$N(CH_2CH_2Cl)_2(CH_2CH_2CH_3)$	24.8	6.5	0.920	4.65	0.93	0.16	..	...
$N(CH_2CH_2Cl)_2((CH_2)_3CH_3)$	24.0	6.4	0.627	3.01	0.95	0.24	..	...
$N(CH_2CH_2Cl)_2(CH_2CH_3)$	23.1	8.6	0.557	2.52	0.10	2.7	8.0	0.20
$N(CH_2CH_2Cl)_2(CH_2CH_3)$ (HN1)	25.0	6.4	0.527	2.79	0.95	0.26	5.8	0.08
$N(CH_2CH_2Cl)_2(CH_2CH_2Cl)$ (HN3)	24.7	4.2	0.31	1.56	1.0	0.44	2.5?	0.0055
$N(CH_2CH_2Cl)_2(CH_2CH_2OCH_3)$	24.6	5.3	0.22	1.09	1.0	0.64	..	...
$N(CH_2CH_2Cl)_2(CH_3)$ (HN2)	24.1	6.23	0.098	0.43	0.90	1.6	5.9	0.02
$N(CH_2CH_2Cl)_2(CH_2CH_2OH)$	21.9?	7.3	0.081	0.313	0.67	3.3	..	...
$N(CH_2CH_2Cl)(CH_2CH_2OH)_2$	...	..	....	....	....	....	6.6	0.13

[a] Relative to methylamine, the dissociation of which was assumed to be the same in 66.7 per cent acetone-water solution as in water. $K_B = 4.6 \times 10^{-4}$; $pK_a' = 10.66$.

TABLE 1 (*Continued*)

Compound	Activation energy in water (kcal/mole)	Conc. = 0.0005-0.0025*M* in water[49]					Conc. = 0.005–0.15*M* in 63.7 per cent acetone in water[18]	
		25 C		37 C			25 C	
		pK_a'	k_1 (min^{-1})	k_1 (min^{-1})	pH = 7.4		Relative* pK_a'	k_2 (min^{-1})
					α	$t_{\frac{1}{2}}$ (min)		
	22.5?	9.3?	0.0094	0.042	0.020	825	..	...
	22.5?	9.2?	0.0068	0.030	0.024	965	..	...

HN2, that the rate was not influenced by a change in the ionic strength of the medium.[11]

The specific rates of cyclization as observed in unbuffered aqueous solution at constant *p*H [20] and in 63.7 per cent acetone-water solution [18] are summarized in Table 1. Tabulated also are the degree of dissociation (α) and the half life ($t_{\frac{1}{2}}$) of each compound in water under physiological conditions of *p*H and temperature (*p*H 7.4 and 37 C). Less precise rate studies [9] made in aqueous bicarbonate buffers at *p*H 7.5–8.5 indicated substantially the same orders of magnitude for k_1 as those found in unbuffered aqueous solution at constant *p*H. The values for k_1 in water include implicitly a factor for the back reaction,[20] but the indications are that this factor is negligible. Observations [61] upon HN2 in 5 and 30 per cent ethanol-water solutions yielded for k_1 the value 0.07 0.08 min^{-1} at 25 C, and 0.31 min^{-1} at 38 C. The order of lability of the homologous tertiary β-chloroethylamines in water is comparable to that reported for *bis*(β-chloroethyl) sulfide (II) and three of its homologs [64] (see Table 7).

In acetone-water solution, the magnitude of k_1 was found [18] to be larger in the following cases: in the case of a stronger base, because it is a better electron donor; in the case of a less hindered base; and in the case of an amine with more freedom of rotation which is not frozen, thus resulting in less entropy decrease on formation of the ethylenimonium ion. Similar general deductions may be drawn from the data obtained in water, although Table 1 discloses an unaccountable irregularity in the distribution of the values of k_1 in acetone-water solution as compared with the corresponding values in aqueous solution.

The effect of change in water concentration upon the cyclization of HN2 in unbuffered acetone-water solution at 25 C is summarized in Table 2.[43a] It may

TABLE 2. Kinetics of cyclization of methyl-*bis*(β-chloroethyl)amine (HN2) in acetone-water solutions.[43a]

Molar conc. of water	Relative value of k_1 at 25 C	Activation energy (E, in kcal/mole)	Log B* (sec^{-1})
1	1	10	3.3
8	10	12	5.8
16	200	17.4	11.05
27	480	17.9	11.73
55.5	1,000†	24.1†	14.9†

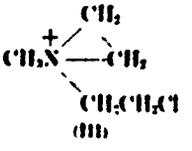
* B = the temperature-independent factor in the Arrhenius equation: $k_1 = B_e^{-E/RT}$

† Calculated from data of Table 1.

be noted that the activation energy of HN2 in pure water is essentially the same as that for the removal of chlorine from a primary alkyl chloride, but that as the water concentration is diminished, the process, although much slower, becomes less temperature-dependent.[43a,55]

20.2.3 Reversal of Cyclization

The formation of HN2 from the 1-methyl-1-(β-chloroethyl)ethylenimonium ion (III)



(III)

in aqueous solution was studied in detail.[43a] This process, the reversal of the cyclization reaction (1a), yielded a bimolecular rate constant (k_{-1}) which was strongly influenced by the ionic strength (μ) of the

solution as defined by the following equation applicable at 37 C; −0.875 is the logarithm of the bimolecular rate constant, $k^{\circ}_{-1} = 0.13$, extrapolated to $\mu = 0$, and −1.0376 is the applicable Debye-Hückel constant:

$$\log k_{-1} = -0.875 - 1.0376\mu^{\frac{1}{2}} + 0.353\mu$$

The distinctive effect of the ionic strength upon the kinetics of the reaction with Cl^-, as well as with $S_2O_3^{--}$ (see Table 3), identified III uniquely as a singly charged positive ion.[28c] This identification is in harmony with theoretical deduction from conductivity measurements,[30,42] and from the composition of the isolated picrylsulfonate of III.[9]

The equilibrium constant for the reversible reaction (1a), in the case of HN2 in water (0.005*M* at 37 C), was found to be $K_{eq} = 3.68$ mole/l at $\mu = 0$, and 6.57 at $\mu = 0.154$ (physiological saline). The latter value corresponds to 97.6 per cent reaction in favor of III at theoretical equilibrium.[28c] The values of the back-reaction constants of the other β-chloroethylamines which have been studied may be deduced from the data given below [see reaction (2a) and Tables 3 and 4].

In 66.7 per cent acetone-water solution, k_{-1} was also found to be sensitive to the ionic strength of the solution.[7,10] For ethyl-*bis*(β-chloroethyl)amine (HN1) and HN2 at 25 C, the values of k_{-1} were determined by graphical and mechanical analysis of the experimental data and found to be 1.5 and 1.4 respectively ($\mu \sim 0.1$). In spite of the temperature difference, these values are of a higher order of magnitude than those found or calculated for water solution at 37 C. Large effects of this kind would be expected in reactions between ions of different sign when the dielectric constant of the medium is lowered, because all effects due to interionic attraction would be increased. For N,N-diethyl-β-chloroethylamine in 66.7 per cent acetone-water solution, k_{-1} is stated to be very low.[10]

Addition of chloride ion (as NaCl) retards the apparent rate of cyclization of HN2 in water;[11] at *p*H 8.0, 30 C, and $\mu = 0.005$–0.10, the data conform to the following empirical linear relation in which −0.652 is the logarithm of k_1 extrapolated to zero chloride concentration:

$$\log k_1 = -0.652 - 0.90\,[Cl^-]^{\frac{1}{2}}$$

20.2.4 Hydrolysis

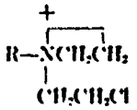
Reaction of the ethylenimonium ion with water proceeds much more slowly than the initial cyclization.[11,40,41] Through the range, *p*H 3.6–8.5, the rate of hydrolysis of III remained constant within the experimental error.[28] The kinetics of the *alkaline* hydrolysis of the ethylenimonium ion have not been adequately analyzed. From the practical standpoint, HN2 can be decontaminated by treatment with excess aqueous alkali for 1–2 hours.[28]

TABLE 3. Kinetics of reactions of imonium ions of nitrogen mustards with H_2O, $S_2O_3^{--}$, and HCO_3^-. The tabulated figures are the bimolecular rate constants, k_{-1} for reaction (2d), and k_2 for reaction (2a). The dimensions of the constants are liter/mole min.

Imonium ion R_1, R_2		Bimolecular rate constants in water at 37 C and constant *p*H[28c]						Bimolecular rate constants in 66.7% acetone-water solution at 25 C[10]
		$\mu = 0.005$	$\mu = 0.000$		$\mu = 0.154$*			$\mu \sim 0.1$
		H_2O *p*H 7.6 $k_{-1} \times 10^3$	$S_2O_3^{--}$ *p*H 4.0 k_2	HCO_3^- *p*H 7.6 k_2	H_2O *p*H 3.6 $k_{-1} \times 10^3$	$S_2O_3^{--}$ *p*H 4.0 k_2	HCO_3^- *p*H 7.6 k_2	H_2O *p*H uncontrolled $k_{-1} \times 10^3$
R_1	R_2							
$-CH_2CH_2Cl$	$-CH_2CH_2Cl$	31.4	13,000†	....	...	2,000†	....	15.
$-CH_2CH_2Cl$	$-CH_2CH_2OH$	5.9†	....	....	...	..	....	...
$-CH_2CH_2Cl$	$-CH(CH_3)_2$	1.39	1,370	0.139	...	207	0.055	...
$-CH_2CH_2Cl$	$-CH_2CH_2CH_3$	0.95	831	0.091	...	128	0.036	...
$-CH_2CH_2Cl$	$-CH_3$	0.90	727	0.079	0.63	112	0.031	0.5
$-CH_2CH_2Cl$	$-CH_2CH_3$	0.67	613	0.067	...	94	0.026	3.0
$-CH_2CH_2OH$	$-CH_3$	0.23‡	.. .	....	..	....	....	...
$-CH_2CH_3$	$-CH_2CH_3$	~ 0.01‡	48	.. .	...	7	....	...

* The constants for $S_2O_3^{--}$ and HCO_3^- are subject to a small correction for change in activity between $\mu = 0$ and $\mu = 0.154$.
† These rate constants are approximations and are probably too low.
‡ Observations made at *p*H 9.

The relative stability of cyclic imonium ions in general permits the direct evaluation of their rates of hydrolysis under suitable conditions. Data are available for seven of these ions at low concentrations in unbuffered aqueous solution at constant *p*H.[11] The bimolecular rate constants at 37 C are given in Table 3. They confirm the report[12] that for the homologous (β-chloroethyl)ethylenimonium ions of the type



the hydrolysis rates in water increase in the following order:

$$R = C_2H_5 < CH_2CH_2CH_2 < CH(CH_3)_2$$

The activation energies for the hydrolysis in water of the 1-(β-chloroethyl)ethylenimonium ions of HN1, HN2, and isopropyl-*bis*(β-chloroethyl)amine were 20 ± 1 kcal/mole within the temperature range of 37–50 C. The heat of activation for the hydrolysis of the 1-methyl-1-(β-hydroxyethyl)ethylenimonium ion was found to be 27 (± 2) kcal/mole within the temperature range of 25–37 C.[29]

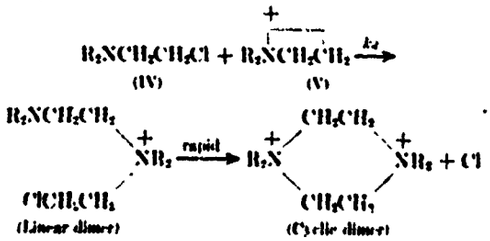
Between *p*H 3.6 and 8.5 (μ = 0.005), the hydrolysis rate of HN in water remained constant,[28a,c] indicating that very low concentrations of OH^- had a negligible effect on the process. Change in μ at low ionic strengths should not affect the hydrolysis rate, but at high ionic strengths (μ = 0.1–0.5) the hydrolysis rate of HN was retarded 12–30 per cent and passed through a minimum.[28c]

A full description of the overall kinetics of *N*-methyl-β-chloroethyl-β-hydroxyethylamine in dilute aqueous solution at *p*H 7.6 and 37 C was obtained with the aid of the experimentally determined constants, pK'_a, k_1, and k_w (k_{-1} assumed negligible).[11] By combining these data with the corresponding values of pK'_a, k_1, and k_w (k_{-1} found negligible) for HN2, the overall kinetics of cyclization and hydrolysis of the latter compound at *p*H 7.6 and 37 C could be fully described[28a] as a series of four successive unimolecular or pseudo-unimolecular reactions. In this description the assumption was made that the two successively formed ethylenimonium ions reacted to a negligible degree under the experimental conditions with the end product, methyldiethanolamine (pK'_a = 8.3). This assumption was subsequently verified analytically.[28b]

In 66.7 per cent acetone-water solution at 25 C, *p*H uncontrolled, the following pseudo-unimolecular values for k_w were reported: *tris*(β-chloroethyl)amine (HN3), ~0.03 min^{-1}; HN1, 0.0057 min^{-1}; HN2, 0.001 min^{-1}.[10,34] These values, corrected for the concentration of water, are recorded in Table 3 and show the expected order of magnitudes, except that the hydrolysis rate of HN1 seems to be unexpectedly high.[10]

29.2.3 Dimerization

The dimerization process (2e) in solutions containing water can be formulated as an initial bimolecular addition, followed by cyclization with the elimination of Cl^-, as follows:



Because of favorable configuration, the transformation of the linear dimer to the cyclic dimer is a rapid process.[2,35] The direct dimerization of two cyclic imonium ions (V) has been suggested,[2] but electrostatic considerations would appear to make it a less likely mechanism. However, since chloride ion is usually present in the system and promotes the reconversion of V to IV (reversal of cyclization), it might appear that direct dimerization had occurred.

In 66.7 per cent acetone-water solutions, k_d at 25 C was found to be 0.40 for HN2, 0.08 for HN1, and apparently very much less for HN3.[7,10] Numerical values of k_d for solutions of nitrogen mustards in pure water are unavailable, but the relative values may be inferred from the data presented in Tables 3 and 4. These data are in accord with the observations that HN3 is much less prone to dimerize than is HN2. In addition, the former more readily undergoes substitution of one of its β-chlorine atoms. These differences are ascribable to the differences between the strengths of the two bases, HN3 being considerably weaker than HN2 (see Table 1).[10,32] In general, the higher homologs of HN2 exhibit less dimerization in aqueous solution than HN2 itself, and as a result these compounds possess greater storage stability.[2] However, it has been pointed out that the extent of dimerization of the higher homologs in a given situation may be limited by their solubilities[11] or by the

balance between their rates of solution and the rates of formation of the corresponding ethylenimonium ions.[42] It should be noted that the data of Tables 1, 3, and 4 were obtained under conditions of concentration that made dimerization a negligible factor.[41]

In certain cases the kinetics of dimerization does not follow the normal second-order course. As an example, in pure liquid HN2, the dimerization rate is stated to be of zero order.[33] This result is evidently due to the fact that the dimer is quite insoluble in this medium and leaves the effective concentration of HN2 constant; hence the dimerization rate would have to be of zero order. The catalytic effects of small amounts of water and oxygen upon dimerization in liquid HN2 have been noted.[31] In dried solutions of HN2 in benzene, the dimerization rate was apparently of the first order; in absolute ethanol, also, HN2 was found to dimerize at a first-order rate (k_d = 0.005 min^{-1} at 25 C; E = 15 17 kcal).[33] In anhydrous benzene and alcohol, the effect of low dielectric constant would be to make the dimerization process (2e) faster than the first-order cyclization process (1a), and the latter would therefore become rate-determining. Hence a first-order kinetics of dimerization would be observed.

The β-chlorine atoms of the cyclic dimers (which are produced as mixtures of stereoisomers)[31] are not readily replaced in acid or neutral solution. In the case of the dimer of HN2, N,N'-dimethyl-N,N'-*bis*(β-chloroethyl)piperazinium dichloride, no observable hydrolysis occurred in aqueous solution at *p*H 4.9 and 38 C; the apparent half life was 23.5 days at *p*H 8 and 4.5 days at *p*H 10.[41] In the case of the dimer of HN1 in aqueous solution at 25 C, excess alkali induced relatively rapid elimination of the two chlorine atoms in two successive bimolecular reactions between the dimer and hydroxyl ion.[10] The reaction liberating the first chlorine atom proceeded more rapidly than did that liberating the second.[10]

At high temperatures (131–178 C) in sealed tubes, the dimer of HN2 in aqueous solutions hydrolyzed slowly at a pseudo-unimolecular rate described by the relation:

$$k = 1 \times 10^{13.7} e^{-23{,}000/RT} \text{ hr}^{-1}$$

It was noted that the *p*H fell from 5 to about 1.5 during the first 15 per cent of this reaction; and there was evidence that side reactions occurred.[42a]

20.2.6 Addition of Electron Donors

The reactions of the imonium ions with electron donors, as exemplified by reactions of the general types (2b) and (2c) and of the special type (2f), are of great importance for the elucidation of physiological mechanisms and for the design of procedures to neutralize toxic derivatives of nitrogen mustards which have gained admittance to tissues and body fluids. The corresponding reactions of the sulfur mustards are likewise of importance and are discussed later.

In general, the reactivity of an imonium ion, as measured by the velocity constants of reactions (2b), (2c), (2d), (2f), and the reversal of (1a), should be reduced by the same structural and energy factors that enhance the velocity of the cyclization process as measured by k_1.[10] However, certain apparent exceptions to this inverse relation are revealed by comparison of the data presented in Tables 1 and 3.

The addition of $S_2O_3^{--}$ and of HCO_3^- to a number of the homologous cyclic imonium ions in water at 37 C was studied in some detail, and the essential results for μ = 0 and 0.154 are shown in Table 3.[29] The thiosulfate derivative (Bunte salt) of HN2 was found to be stable in solution.[9,41] The corresponding dipropionic acid ester was relatively unstable ($t_{\frac{1}{2}} \sim 3$ hours at *p*H 7.4 and 37 C),[29] and the carbonic acid ester was too unstable for isolation or confident measurement.[9,25a] An important deduction derived from these data and observations on phosphates[9] is that certain buffers can and do interact with the cyclic imonium ion. The *relative* values of k_2 in Table 3 for the reactions of the various imonium ions with $S_2O_3^{--}$ are substantially the same as those for the reactions with HCO_3^-. The same is true for the relative values of k_w, an indication that the discriminating ability of these cyclic compounds is not affected by the differences in structure which they exhibit. This correspondence would be expected to hold for any other reactions of the imonium ions which proceed by the same mechanism under the same conditions. A comparable situation, revealed by "competition factors" for substances reacting with derivatives of sulfur mustards, is discussed later.

The bimolecular rate constant (k_2) for the reaction of the 1-methyl-1-(β-chloroethyl)ethylenimonium ion (III), derived from HN2, with other electron-donating groups (including Cl$^-$, for which $k_2 = k_{-1}$) were determined at 37 C and μ = 0 and 0.154. They are shown in Table 4.[29] As indicated above, from such data one may estimate the corresponding values of k_2 for the other imonium ions listed in Table 3.

The reaction of the cyclic ethylenimonium ion with amines and tetramines, as exemplified by reaction

TABLE 4. Kinetics of reactions of 1-methyl-1-(β-chloroethyl)ethylenimonium ion (III) with electron donors at 37 C. Original sources of data are given in the bibliography.[28]

Electron donor	pH	Bimolecular rate constant (k_2, in l/mole min) $\mu = 0$	$\mu = 0.154$
Chloride	3.6	0.133	0.064
Propionate	7.4	0.13	0.051*
Benzoate	7.4	0.12	0.047*
	8.4		
dl-Alanine carboxylate	6.0	0.1–0.2?	....
Thiocyanate	8.0	Approx. 3 (30 C)	....
Methyldiethanolamine	7.4	10?	....
	8.4		

* Not corrected for activity at $\mu = 0.154$.

(2f), has been shown to occur more or less readily.[6] In the case of tertiary amines, there are indications that the steric configuration of the substituents modifies the accessibility of the amine nitrogen and thus influences its rate of reaction with the imonium ion.[28] This fact would have an obvious bearing on the kinetics of the terminal reactions of the nitrogen mustards in water.

20.3 β-CHLOROETHYLAMINES IN HETEROGENEOUS SYSTEMS

The behavior of the β-halogenated ethylamines in water suspensions of suitably activated carbons is of interest from the standpoints of physiological mechanisms and of decontamination of water. Two primary amines, β-bromoethylamine and β-phenyl-β-chloroethylamine ($C_6H_5{\cdot}CHCl{\cdot}CH_2NH_2$) have been so studied. It was found in each case that the rate of cyclization of the amine in alkaline solution was slower, and the reverse process in acid solution was faster in the presence of Merck's blood charcoal than in its absence.[47,49] This finding is in agreement with the general rule that the formation of adsorbable substances is favored at interfaces, i.e., the shift of equilibrium at an interface is positive with a decrease in surface energy. Each of these primary amines was more strongly adsorbed than its more soluble ethylenimonium ion, and, in neutral solutions containing carbon, the equilibrium (amine $\rightleftharpoons$ cyclic product) was strongly shifted toward the amine.

The cyclization of β-phenyl-β-chloroethylamine (half life of approximately 4 minutes in homogeneous solution) was only 85 per cent complete at 18 hours in the presence of activated carbon. At 25 C, the rate constant in the heterogeneous system was 1/70 of that in homogeneous solution, and at 37 C the corresponding ratio was 1/20.[49] The fact that the temperature coefficient of the cyclization was lower in the presence of suitable carbon than in its absence is direct evidence that the reaction was taking place at the interface. The kinetic data obtained at different temperatures permit the calculation of the values of E and B in the Arrhenius equation, $k_1 = Be^{-E/RT}$ for the reactions in the homogeneous and heterogeneous systems. These values are shown in Table 5.

TABLE 5. Kinetics of cyclization process of β-halogenated amines in homogeneous solution and in heterogeneous systems containing activated carbon.

Compound	Type of activated carbon present	E (kcal)	Log B (sec^{-1})
$C_6H_5CHClCH_2NH_2$	None	20	12.4
	Blood	~20	11.1
	Carboraffin	13.5	6.2
$BrCH_2CH_2NH_2$	None	25	14.0
	Blood	19.3	10.4

The decrease of E would tend to accelerate the rate of cyclization, but the proportionately greater decrease of B results in a net retardation of the reaction in the presence of the carbon.[49]

The above observations on primary amines seem to be corroborated generally by reports on the adsorbability of the tertiary β-chloroethylamines and their products from water solutions onto activated charcoal.[11] HN3 and triethanolamine appear to be efficiently adsorbed, but "DB3-positive material" (presumably ethylenimonium compounds) was hardly adsorbed at all. The same holds for HN1, except as modified by its greater solubility and by the greater stability of its polar 1-ethyl-1-(β-chloroethyl)ethylenimonium ion.[27]

20.4 CORRELATION OF TOXICITIES OF β-CHLOROETHYLAMINES WITH KINETICS OF THEIR CYCLIZATION

It has been noted[20,28] that a good correlation exists between the subcutaneous toxicities[4] for mice of the hydrochlorides of a number of tertiary and secondary β-chloroethylamines and the half lives of the amines in aqueous solutions under physiological conditions of pH and temperature (37 C, pH 7.4). The shorter the half life of the amine, the greater its toxicity. A comparably clear-cut correlation does not exist between the subcutaneous toxicities of the hydrochlorides and the reactivities of the first-step

ethylenimonium ions of the amines. The possible implications of these and other correlations between toxicity and the properties of sulfur and nitrogen mustards and their derivatives are discussed in Chapter 22.

20.3 SULFUR MUSTARDS IN HOMOGENEOUS SOLUTION

As indicated by the scheme presented in Section 20.1, the reactions of the sulfur mustards are qualitatively similar to those of the nitrogen mustards. Evidence will be presented to show that cyclization occurs (as with the nitrogen mustards) by a thermally activated solvolytic mechanism. The onium ion, in this case an ethylenesulfonium ion, which is thus formed then reacts with water and other uncharged nucleophilic molecules and with anions to form various products. The reaction sequence is repeated if the sulfur mustard contains a second β-chloroethyl group. Thus, one may write for a typical sulfur mustard, $RSCH_2CH_2Cl$, the following reactions, which correspond to reactions (1a), (2d), (2e), and (2f) given on page 417 for a typical nitrogen mustard:

$$RSCH_2CH_2Cl \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \overset{+}{\underset{\frown}{RSCH_2CH_2}} + Cl^- \qquad (1b)$$

$$\overset{+}{\underset{\frown}{RSCH_2CH_2}} + H_2O \xrightarrow{k_w} RSCH_2CH_2OH + H^+ \qquad (2g)$$

$$\overset{+}{\underset{\frown}{RSCH_2CH_2}} + RSCH_2CH_2Cl \xrightarrow{k_4} \text{dimers} \qquad (2h)$$

$$\overset{+}{\underset{\frown}{RSCH_2CH_2}} + RSCH_2CH_2OH \xrightarrow{k_5} \overset{+}{RSCH_2CH_2SCH_2CH_2OH} \qquad (2i)$$

$$\qquad\qquad\qquad

a second, successive, first-order reaction involving the second β-chloroethyl group.

3. In unbuffered solution the apparent rate of hydrolysis of H is *p*H-independent over the range of *p*H 3 11.[46,54]

4. Various substances, including those usually used to buffer solutions, can react with activated H and modify the course of the overall reaction. Indeed, some anions (e.g., monothiophosphate) react so much more rapidly than does water that in their presence little or no hydrolysis (formation of thiodiglycol and acid) occurs.[18,41a] Nevertheless, the overall rate of disappearance of H is not altered by the presence[1,54] of such substances.[b] In other words, this rate is determined solely by the concentration of H and the temperature of the solution.

5. The addition of chloride ion (as NaCl) in moderate concentration retards the rate of disappearance of H without altering the final outcome of the reaction as measured by the production of 2 equiv of acid per mole of H.[39a,41a] The quantitative effects of different concentrations of added chloride ion are in accord with the concept that reversal of the activation process occurs by the bimolecular reaction [reaction (1b)] of the activated H with chloride ion.[18]

6. The apparent rate of hydrolysis of H is not altered in the presence of metallic catalysts (e.g., Ag^+, Cu^{++}, Mn^{++}, Ni^{++}, Fe^{+++}).[6,53]

7. In solvents less polar than water, the reactions of H are markedly retarded.[6,53,54]

8. In accordance with the concept that the reactions of H in water involve an initial solvolytic step, vapor phase hydrolysis does not occur to an appreciable extent.[1]

The above observations indicate clearly that H and related β-chloroethyl sulfides undergo a monomolecular rate-determining transformation consisting of a solvolytic ionization into chloride ion and a positively charged ("activated") residue. The latter has been regarded as the primary carbonium ion, $RSCH_2CH_2^+$.[41a,b] However, no evidence is available that primary alkyl halides undergo a monomolecular solvolysis of this type. Moreover, the activated intermediate from H differs from those usually encountered in solvolytic reactions in that it retains the ability to discriminate between the various substances with which it may react. As a consequence, it has been suggested[1,2] that the activated carbonium ion postulated above is stabilized by ring formation to a virtual or actual ethylenesulfonium ion, $RSCH_2CH_2^+$. Such an ion must be reactive because of its ring strain, but it must be considerably more stable than the simple carbonium ions postulated to occur in the hydrolysis of secondary and tertiary alkyl halides.

The postulated mechanism, which permits the carbon atom to attain a normal octet of valence electrons by sharing a pair with the sulfur atom, has persuasive chemical analogies,[57] the closest being the formation of the ethylenimonium ion in the case of the nitrogen mustards (see Section 20.4).[c]

20.5.2 Kinetics of Overall Reaction of *bis*(β-Chloroethyl) Sulfide in Aqueous Solution

Although the hydrolysis of H in water proceeds as a succession of reactions, the major part of the total reaction, $S(CH_2CH_2Cl)_2 + 2H_2O \longrightarrow S(CH_2CH_2OH)_2 + 2HCl$, can be described as a single, quasi-monomolecular process.[51,54] The rate constant for this process (or its initial portion) as determined by measurement of acid liberation will be designated as k_1. Much of the information on the reactivity of H has been acquired through the use of this approximation. Accordingly, representative results have been brought together in Table 6. The data reveal the characteristic temperature coefficient for the overall process. The conspicuous retardation in sea water as compared with the rate of reaction in pure water may be related to the chloride ion concentration of the former.

20.5.3 Kinetics of Formation of Ethylenesulfonium Ion

The rate of formation of the postulated ethylenesulfonium ion from solutions of β-chloroethyl sulfides in water has been determined directly by measuring the rate of evolution of chloride ion, and indirectly by measuring the rate of acid production. As stated above, the latter procedure is valid because hydrolysis is very rapid compared with the rate of the cyclization reaction (i.e., $k_w >> k_1$). An alternative experimental procedure has been to determine directly

[b] Purported acceleration of the rate in the presence of monothiophosphate ion has been disproved.[39,41]

[c] It is of interest that the displacement of chlorine in the oxygen analog of H, *bis*(β-chloroethyl) ether, proceeds by an entirely different mechanism. There is no evidence for the existence of a monomolecular activation step to form an onium compound.[12] The reaction is bimolecular. For reaction with OH^-, $k_2 = 0.033$ l/mole min; for reaction with $S_2O_3^{--}$, $k_2 = 0.32$ l/mole min.

TABLE 6. Apparent rate constants (k_1) for hydrolysis of sulfur mustards in water. Medium usually contained 1–5 per cent ethanol or isopropanol.

Compound	Medium	Temp (°C)	k_1 (min^{-1})	$t_{\frac{1}{2}}$ (min)	References	Notes
bis(β-Chloroethyl) sulfide (H)	Water	0.6	0.0044	158.0	51	Data not consistent due to inadequacy of sampling procedure.[3]
		10.0	0.012	57.8		
		20	0.047	14.7		
		30	0.21	3.3		
		37.4	0.27	2.6		
		12.5	0.0215	32.2	52	E = 17–18 kcal. Values uniformly low as though from systematic error. Used quinhydrone electrode.
		20	0.044	15.8		
		30	0.118	5.9		
		40	0.261	2.7		
		50	0.646	1.1		
		14.5	0.028	24.8	54	E ~ 20.8 kcal. Titrimetric, indicator.
		24.6	0.097	7.1		
		36.8	0.355	2.0		
		25.0	0.121	5.7	3	Titrimetric, indicator.
		30.0	0.219	3.2	23a	Tritimetric, glass electrode.
		20	0.094	7.4	41g	E ~ 22.8 kcal. Titrimetric.
		25	0.176	3.9		
		30	0.342	2.0		
		25	0.176	3.9	33	Titrimetric.
	Sea water	25	0.012	60	40	Titrimetric, indicator.
		30	0.028	25	23b	Titrimetric, glass electrode.
1,2-*bis*(β-Chloroethylthioethane (Q)	Water (extrapolated)	25	~ 0.4	1.7	21	Extrapolated to water from following experiment.
	32% dioxane in water	28	0.086	8.1	21	.....
bis(β-Chloroethylthioethyl) ether (T)	Water	25	0.212	3.3	39	pH = 3.8–4.2. E = 20 kcal.
	Water	25	0.248	2.8	41d	5% ethanol present. pH = 5–8.

TABLE 7. Kinetics of ionization of β-chloroethyl sulfides at 25 °C.

R·SCH$_2$CH$_2$Cl (R)	Medium	k_1 (min^{-1})	E (kcal)	Reference	Notes
HOCH$_2$CH$_2$–	Water	0.106	16.8	37	Glass electrode. pH
	<1% ethanol in water	0.30	...	29b	Selective extraction of ClH
	5% ethanol in water	0.23	...	41e	Titration of acid
	.....	0.235*	...	41e	Computed from k_1 = 0.171
	5% acetone in water	0.260	...	18	Determined acid and chloride; μ = 0.144
ClCH$_2$CH$_2$–	Water	0.118*	18.5	38	Glass electrode. pH
		0.16	...	29a	Selective extraction
	5% acetone in water	0.155*	...	18	Determined acid and chloride; μ = 0.144
CH$_3$CH$_2$–	5% ethanol in water	0.090	...	41d	Titration of acid
CH$_3$CH$_2$CH$_2$–	5% ethanol in water	0.090	...	41d	Titration of acid
C$_6$H$_5$–	5% ethanol in water	0.028	...	41d	Titration of acid
C$_6$H$_5$CH$_2$–	1% ethanol in water	0.200	19.5	23b	Titration of acid
	20% ethanol in water	0.144	...	41g	Titration of acid
$^{-}$O$_3$PCH$_2$CH$_2$–	5% acetone in water	0.70*	...	18	Titration of acid

* Calculated from the appropriate equations for two consecutive first-order processes.

the selectively extracted H and ClH after various reaction times.[29a]

Table 7 summarizes the available observations for the simpler β-chloroethyl sulfides in water, ethanol-

water, and acetone-water solutions. In general, the reaction rate follows a first-order course and is determined by k_1 in reaction (1b). The reverse reaction is negligible under these conditions.

It will be noted that in the cases of H and CH the reaction rate as determined from changes in *p*H appears to be lower in water than in ethanol-water or acetone-water solutions. It may be suspected that the difference is due to experimental errors. If the difference were real, it would signify that, contrary to general observation, the organic solvents accelerated the ionization rate. In addition, it will be observed that the reaction rates in water as determined by the procedure of selective extraction of H and CH[2m,b] are higher than those determined by means of the changes in *p*H.[37,38]

In the case of H and CH in 5 per cent acetone-water solution, the reaction rate was not significantly influenced by changes in ionic strength induced by addition of an inert salt (sodium benzenesulfonate), and the small amount of chloride accumulating as a reaction product had no detectable effect on the kinetics of the process.[18]

20.3.4 Reactions of Ethylenesulfonium Ion

Since the hydrolysis of H and CH [reaction (2g)] proceeds within experimental error as rapidly as the rate of formation of the ethylenesulfonium ion, k_w must be relatively great. An accumulation of as much as 3 per cent of ethylenesulfonium ion could occur if k_w were 30 times greater than k_1. As the maximum probable accumulation is not more than 1 per cent, k_w should be at least 100 times as large as k_1.[18]

From the standpoint of detoxification of the sulfur mustards in tissues and body fluids, the reactions of ethylenesulfonium ion with anions are of great importance. These reactions are typified by the generalized reaction (2a). The participation of chloride ion in the bimolecular reversal of cyclization [reaction (1) or (1b)] is a special case which may be treated first.

A quantitative estimate of the absolute rate of reversal of cyclization is not possible, because the rate constant (k_{-1}) is inextricably associated with the rate constant of hydrolysis (k_w), and the latter is too high to be measured in any of the systems that have been investigated.

As indicated above, added chloride ion retards the apparent hydrolysis rate of H without altering the end result.[2m,4b] This means that the available ethylenesulfonium ion, which is reacting simultaneously with Cl^- to form H and with water to liberate hydrogen ion, produces acid at a lower rate in the presence of added chloride than it would in water alone. The retardation of hydrolysis may be described either by an empirical linear relation [equation (3)],[39] or as a ratio of apparent hydrolysis rates derived with reasonable assumptions from the kinetic laws for two successive monomolecular reactions [equation (4a)]. In equations (3) and (4a), k_1 and k_1' represent the intrinsic rate constants respectively in water and in water plus added Cl^-, and k_2 and k_2' are the corresponding apparent rate constants as experimentally determined by measurement of acid production over the first 5–20 per cent of the overall reaction (see Table 6). In practice, k_2'/k_2 has been assumed to be equal to k_1'/k_1.

$$\log_{10}\frac{k_2'}{k_2} = -1.516[Cl^-] \quad \text{(for 30°C)} \tag{3}$$

$$\frac{k_1'}{k_1} = \frac{1}{1 + F_{Cl}[Cl^-]} \tag{4a}$$

$$\frac{\text{Hydrolysis rate in presence of competitor X}}{\text{Hydrolysis rate in water}} = \frac{1}{1 + F_X[X^-]} \tag{4b}$$

F_{Cl} is termed "the competition factor of chloride ion," and provides a measure of the reactivity of the chloride ion toward the ethylenesulfonium ion, as compared with that of water. The competition factor F_X for any anion X^- is formulated in the same way; and by appropriate modifications of the type equation represented by equation (4b), the competition of mixtures of hydrolysis-inhibiting substances can be formulated in terms of their respective concentrations and specific competition factors.[4b]

The empirical relation (3) is inadequate in that it predicts unreasonably increasing values for the reactivity of chloride ion as the ionic strength approaches zero.[18] The competition factor equation (4a) is not precise either, for its use gives values of F_{Cl} which vary with chloride ion concentration.[2m,4a] Although this equation correctly assumes that the relative rates of combination of anions with ethylenesulfonium ion depends only upon their chemical natures and relative concentrations, it does not take into account the effect of ionic strength upon these bimolecular reactions. Since F_X represents a function of the ratio of the rate constants for the reactions of the cation, ethylenesulfonium, with uncharged water and with negatively charged anion, respectively, F_X should be sensitive to change in ionic strength. Furthermore, precise calculations of F_X by use of equa-

tion (4b) require exact knowledge of the values of k_1 and k'_1. These values are usually approximated as the initial rates (k_r and k'_r) of the respective processes at zero reaction time. The approximations may be very close at low temperatures, but at 25 C and higher the errors may become appreciable. Thus, at 25 C with H, k_r is about 5 per cent too high if calculated from the origin to $t = 0.5$ minute, and 10 per cent too high if calculated to $t = 1$ minute; and in the presence of monothiophosphate ion, the errors in k'_r calculated for these time intervals are 14 and 26 per cent, respectively.[18] It may be suspected that this source of error accounts, in part at least, for the rather wide discrepancies between the k_r values reported by various observers (see Table 6).

In spite of these inherent sources of error, the orders of magnitude of the competition factors for various anions are significant. Determination of the relative values for a wide variety of compounds[3,4b] has been of great practical value in furnishing a basis for the selection of those classes of substances likely to serve as effective detoxicants of H. It has also provided a general index of the relation of chemical structure to the electron-donating strength of compounds possessing unshared electron pairs, as may be illustrated by the examples given in Table 8.[3] In

TABLE 8. Illustrative competition factors.

Anion (X^-)	Competition factor (F_X)
Dithiophosphate	130,000
Thiosulfate	27,000
Phosphate	75
Sulfate	7.3

view of their possible deep-physiological significance, the unique position of thiol compounds as strong competitors should be emphasized. A complete table of competition factors is given in Chapter 19.

It merits emphasis that addition of substances with high competition factors does not accelerate the rate of disappearance of H from aqueous solutions, but merely alters the final products of the overall reaction. The reaction in the presence of thiosulfate provides an example.[1,34] The two ethylenesulfonium ions formed in succession by an H molecule react with the thiosulfate ion to produce the Bunte salt, $S(CH_2CH_2SSO_3)_2$. The rate of the process is essentially the same as for the production of thiodiglycol (i.e., hydrolysis) in pure water, but in this case virtually no hydrolysis occurs.

The quantity which is of significance for an accurate description of the rates of reaction of anions with ethylenesulfonium ion is not the competition factor as above defined, but rather the rate constant of the particular competing agent relative to that of water at some standard ionic strength. For chloride ion such a constant has been defined as the "relative rate constant of chloride ion at ionic strength μ," as follows:[14]

$$(r_{Cl^-})_\mu = \left(\frac{k_{-1}}{k_w}\right)_\mu$$

In this equation k_{-1} is the second-order rate constant for the reaction of ethylenesulfonium ion with chloride ion, and k_w is the pseudo-first-order rate constant for its reaction with water. In the case of both H and CH, (r_{Cl^-}) has a value of 18 ± 2 at $\mu = 0.144$ and attains a limiting value of 34 ± 4 at $\mu = 0.000$. At constant μ these values are independent of chloride ion concentration.

The dimerization of β-chloroethyl sulfides to the corresponding linear sulfonium and cyclic 1,4-dithionium compounds according to reaction (2h) has not been encountered. In the case of the nitrogen mustards, the corresponding compounds are formed to an appreciable extent (see previous discussion and Chapter 19). With H, however, the relatively low basicity of the sulfur atom would make such combinations very unstable.[4a]

As indicated by reaction (2i), the additions (sometimes incorrectly termed polymerizations) of ethylenesulfonium ions and thiodiglycol (TG) occur readily in aqueous solutions. The sulfonium compounds, H-TG, H-2TG, and CH-TG are formed (see Chapter 19). It will be noted that only the first of these three compounds contains a β-chloroethyl group. The formation of sulfonium salts is favored when the initial concentration of H is high.[4,16] These additions also occur in anhydrous mixtures of H and TG,[16] but at lower rates than in aqueous solutions.

The bimolecular reactions which result in the formation of the sulfonium compounds have not been subjected to systematic kinetic analysis. The chemical reactions of the compounds are discussed in Chapter 19.

20.3.3 Reaction Kinetics of Sulfoxides, Sulfones, and Mustards with Two Sulfur Atoms

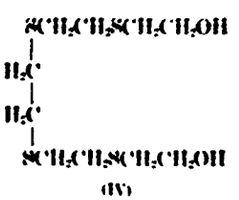
H sulfoxide, $(ClCH_2CH_2)_2SO$, is relatively resistant to hydrolysis;[28,33] the reaction proceeds only very slowly at *p*H 8.[17]

H sulfone, $(ClCH_2CH_2)_2SO_2$, also resists hydrolysis in unbuffered aqueous solution,[28] but its conversion to divinyl sulfone, $(CH_2{=}CH)_2SO_2$, and HCl is catalyzed by hydroxyl ion. Upon the addition of sodium hydroxide, 0.55 equiv of chloride ion and of acid per mole of H sulfone was liberated in 90 minutes at *p*H 6.5-7.0, and, at *p*H 7.5-7.8, 1 equiv of chloride ion and acid appeared within 3 minutes.[17] On the other hand, in the presence of bicarbonate at *p*H 7.5-7.8 the reaction was markedly retarded (to one-fiftieth or less of the above rate).[17]

Divinyl sulfone does not react detectably with water in neutral aqueous solution, and reacts only very slowly at *p*H 8.4.[17]

1,2-*bis*(β-Chloroethylthio)ethane (Q or sesquimustard) in 32 per cent dioxane in water solution hydrolyzes at a rate comparable to that of H in water (see Table 6).[21] The initial liberation of acid follows a first-order course for which $k_1 = 0.086 \pm 0.006$ min^{-1} at 28°C. This apparent rate increases with increase in the water content of the reaction mixture, varying as the fourth power of the water concentration. Extrapolation to pure water gave $k_1 \sim 0.4$ min^{-1}. A second, much slower stage of acid liberation has also been observed and related to the hydrolysis of the second β-chloroethyl group. For this, $k_1 = 0.00396$ min^{-1} in 32 per cent dioxane in water.[21]

There is evidence to indicate that under certain conditions Q, like H, can react with the products of its own hydrolysis to form sulfonium salts. In contrast to the sulfonium salts of H, some of the sulfonium salts of Q appear to be unstable. For example, pentaethylenetetrasulfide-ω, ω′-diol (IV)



(IV)

has been isolated after hydrolysis of Q by 50 volumes of water (see Chapter 19).

Q sulfone in either pure water or bicarbonate solution undergoes no detectable hydrolysis for at least 1 month.[21]

bis(β-Chloroethylthioethyl) ether (T) appears to hydrolyze in two stages and at an even more rapid rate than H or Q.[19] The data shown in Table 6 relate to the first stage. In the case of one estimate,[29] the value for k_1 was arbitrarily determined from the slope of the straight part of the log concentration versus time curve; in the case of the other entry,[30] the initial value of the slope was used as the basis of the estimate.

20.5.6 Kinetics of Oxidation of *bis*-(β-Chloroethyl) Sulfide (H) by Peroxides

In methanol-water solution, the oxidation of H by urea peroxide and H_2O_2 is slow and accompanied by solvolysis with resultant acid production and increase in the bimolecular rate constant. With urea peroxide in 84.4 per cent methanol in water, $k_2 = 0.0018$-0.0083 l/mole min; with H_2O_2 in 66.7 per cent methanol-water, $k_2 = 0.012$-0.023 l mole min. The results indicate that H_2O_2 and salts yielding H_2O_2 are not active enough to be useful for decontamination under physiological conditions.[8]

The oxidation of the sulfur of H to the sulfone state should tend to reduce the strength of binding of the β-carbon atom, and in the case of *bis*(β-pyridinium ethyl) sulfone, the binding was found to be such as to permit the direct observation of a reversible reaction which was catalyzed by OH^-.

$$O_2S(CH_2CH_2\text{-}\overset{+}{N}C_5H_5)_2 + 2OH^- \rightleftharpoons O_2S(CH{=}CH_2)_2 + 2C_5H_5N + 2H_2O$$

At lower *p*H, the equilibrium was forced toward the left, and at higher *p*H toward the right.[17]

20.6 KINETICS OF SULFUR MUSTARDS IN HETEROGENEOUS SYSTEMS

In heterogeneous systems such as occur in tissues and on moist terrain, the various phases and interphases provide numerous possibilities for the distribution of compounds such as H, its intermediates, and its reaction products. Under such circumstances no rational physicochemical picture of the detailed behavior of H or any other persistent agent is possible at the present time.

It merits mention that for some systems (e.g., moist terrain contaminated with droplets of a sulfur mustard), the hydrolytic and other reactions discussed in the preceding sections have little practical bearing on the persistence of a hazard for troops. The limiting physicochemical factors are the rates of evaporation and of solution.[26]

Blood and plasma are relatively simple heterogeneous biological systems in which the apparent rates of disappearance of H and ClH have been studied (see Table 9). The entries of the table suggest the exist-

ence of a species variation. They indicate also that the rates of disappearance from the blood or plasma of different individuals of a given species exhibit a notable variation and are, in general, lower than the rates of disappearance at the same temperature from homogeneous solutions containing the same concentration of chloride ion.

The rates of disappearance of both H and CH are lower in whole blood than in plasma. It follows that the cellular elements of blood must participate in the removal of H and CH from the extracellular phase.[12] However, it is apparent that the removed agent is not destroyed so rapidly as that which remains in the plasma. Presumably reversible adsorption with or without solution in nonaqueous phases plays a role in this phenomenon.

TABLE 9. Apparent rates of decomposition of bis(β-chloroethyl) sulfide (H) and β-chloroethyl β-hydroxyethyl sulfide (CH) in whole blood and in plasma.

The data were obtained by selective extraction and subsequent determination of H and CH. The apparent rates of decomposition are tabulated in terms of the apparent first-order rate constant (k_r) and the half life ($t_{\frac{1}{2}}$). In the case of H, k_r refers to the first ionization step.

Agent	Species	Medium	Anticoagulant	Temp (C)	k_r (min^{-1})	$t_{\frac{1}{2}}$ (min)	Reference
H	....	0.9% NaCl	.....	25	0.037	19	22
	Man	Blood	Citrate	25	0.03–0.04	17–21	20
	Man	Plasma	Citrate	25	0.026	27	20
	Man	Blood	Heparin	25	0.014–0.023	30–50	22
	Sheep	Blood	Heparin	25	0.03	24	22
	Rabbit	Blood	Heparin	25	0.012–0.014	50–60	22
	Rabbit	Blood	Heparin	25	0.009	74	20c
	Rabbit	Blood	Heparin	37	0.05	14	20c
	Rabbit	Blood	Heparin	37	....	8+	13
	Rat	Blood*	Heparin	37	0.054	12	44
	Dog	Blood	Oxalate	25	0.02–0.03	27–35	22
CH	Rabbit	Blood	Heparin	25	0.12	5.8	20b
	Rabbit	Blood	Heparin	37	0.53	1.3	20b
	Rabbit	Plasma	Heparin	25	0.085	8.2	20b

* Equilibrated with 5 per cent CO_2.

Chapter 21

EFFECTS OF SULFUR AND NITROGEN MUSTARDS ON PROTEINS, ENZYMES, AND CELLS

By *Milton Levy* *

21.1 INTRODUCTION

THE PRACTICAL OBJECTIVES of the work reviewed in this chapter have been set forth in Chapter 19, Section 19.1. The present chapter reviews the work falling between the strictly chemical studies (Chapters 19 and 20) and the investigations on the mechanism of cutaneous and systemic injury in animals and man (Chapters 22 and 23).

The primary scientific objective in the work described in this chapter has been the development of a theory of vesicant action in cellular terms. Several desiderata for such a theory are evident. It must provide for rapidity of reaction of the vesicant and for the delay in the development of grossly visible damage.[2] It must account for the effectiveness of low dosages of vesicant. It must account for the relationship between the quantity of vesicant and the qualitative and quantitative nature of the resulting damage. The hope appears vain that a single reaction resulting from a vesicant may be found responsible for all subsequent events in the development of injury because the studies on many systems have shown that the reacting groups are multiple. It is, therefore, to be expected that the discovery of an especially sensitive material may indicate the minimal reaction for damage without explaining all the observed effects as the vesicant concentration or time of exposure is increased.

Although some actions of vesicants in various doses may be the result of acid liberated through hydrolysis,[39a,48] the acid hypothesis [61] has been rejected as inadequate.[22,39b,40,64] The suggestion that delay in action is related to a necessary preliminary formation of a sulfone (H sulfone or divinyl sulfone from mustard) [48] has been discussed.[22,36–38,39b,c] Estimates of the oxidation potential required to accomplish this change [27] indicate that living cells would not be able to bring it about to an appreciable extent.

It seems generally agreed that a rapid reaction with protein material [34,39b,c] (see Chapter 19) is the most likely primary chemical event of biological interest. There appears to be no real necessity for a strictly chemical mechanism acting on the vesicant to explain the delayed onset of detectable injury. The delay is sufficiently explicable in terms of the existence of noninstantaneous processes in normal functioning. Any delay in manifestation of the action of a vesicant can be described as the time required for the defect or derangement produced by the rapid chemical action to be effectuated in a demonstrable manner through otherwise normal mechanisms. On this basis, the postulation of protein compounds which may slowly release unchanged vesicant [34] is an unnecessary complication, and parallelism of development of lesion to enzyme inactivation [27b] may occur if the latter is a result rather than a cause of pathological changes.

A very common phenomenon resulting from the action of vesicants in very small amounts is inhibition of cellular reproduction. Corneal epithelium, regenerating liver, yeasts, tissue cultures, tumors, and marine eggs show one form or another of delayed reproduction when treated with vesicants. With marine eggs, the most marked delay is in early prophase. In so far as is known, the delay in the case of other kinds of cells is at a corresponding phase of the cellular reproductory cycle. In general, effects on gross metabolism require more drastic treatments than those that suffice to inhibit cellular reproduction.

Delayed reproduction points to effects involving nuclear material. Additional evidences of nuclear involvement have been obtained by study of nuclei and chromosomes in vesicant-treated material, and from the finding that vesicants prevent the swelling of isolated nuclei suspended in sodium dioctylsuccinosulfate solutions.

Loosening of corneal epithelium is a result of derangement of corneal metabolism produced by vesicants. The alteration seems to involve an increased proteolysis.

Reaction of the vesicants with proteins have been shown to alter the physical properties (solubilities, acid-base behavior), the catalytic properties (enzymatic activity), and the biological properties (im-

* Of New York University College of Medicine.

munological reactions) of the protein. Studies on enzymes tend to dissociate *in vitro* and *in vivo* sensitivities. It should be emphasized that the *in vitro* results with proteins and enzymes have generally involved relatively high concentrations of the reacting vesicants.

A difficulty which persists is the evaluation of experimental results in terms of the doses to which the whole organism might be subjected. In most of the experimental work, the controlled concentrations of vesicants have been used in as nearly uniform media as possible. The presence of a lipid phase and of membranes, and the subsequent, probably nonuniform, distribution to all parts of the body prevent a simple extrapolation of the results of *in vitro* studies to multicellular organisms.

21.2 REACTIONS OF PROTEINS WITH VESICANTS

21.2.1 Reactive Groups of Proteins

As would be suggested by the reactions of the sulfur and nitrogen mustards with amino acids and other simple compounds of biochemical interest (Chapter 19), certain functional groups of proteins react with these vesicants. The reactions are *p*H-dependent because the active forms of the toxic agents are positively charged ethylenesulfonium and ethylenimonium ions (Chapters 19 and 20) which presumably react only with uncharged or negatively charged protein groups. At physiological *p*H (6.0–8.0), carboxyl, imidazole, thiomethyl, and sulfhydryl groups react to a significant extent. A few amino groups also react. Phenolic and aliphatic hydroxyl, indolyl, guanido, and most amino groups do not react.

At *p*H 5.5–6.0, *bis*(β-chloroethyl) sulfide (H) reacts with all or most of the carboxyl groups of proteins.[4,10] At *p*H 6–8, imidazole groups react.[4] At *p*H 6, few or none of the amino groups react.[10] If the actions occur in alkaline media, however, amino groups do react.[23] In the action of butyl β-chloroethyl sulfide (butyl-H) on insulin, about 3 per cent of the reacting butyl-H can be recovered attached to the amino group of phenylalanine,[12] suggesting that at the *p*H of treatment (7.4–7.6) the terminal amino groups derived from phenylalanine are only partially in the ionic state.

Study of the dietary availability of the amino acids of casein treated with H at alkaline reaction shows that its lysine, histidine, methionine, and threonine become unavailable for rats.[20k] Addition of arginine, lysine, and cystine does not adequately supplement this H-treated casein for chicks.[20l] If the casein is treated at neutrality, only methionine and threonine become unavailable for rats.[20j] The threonine is made available by acid hydrolysis, whereas methionine is not. The probable interpretation is not that the hydroxyl group of threonine reacts with H, but rather that this amino acid fails to be liberated in absorbable form by the action of digestive enzymes on the H-treated casein.[20j] So interpreted, the results conform to the demonstrated nonreactivity of the hydroxyl groups of serine and threonine with H (Chapter 19). Bacteriological assay also shows the special reactivity of methionine and a lesser sensitivity of lysine in casein.[20m]

The possible reactions of the phenolic and indolyl groups in protein are obscure. These groups are responsible for the reduction of the Folin phenol reagent by proteins. The reagent is reduced to a lesser extent by H protein than by native protein at *p*H 8.0, but the difference disappears when the reduction takes place in more alkaline medium[10,12] or in the presence of detergent.[12] These factors also increase the reduction caused by many native proteins. If a reaction of H with phenolic groups were to occur, there would be formed an ether which would, in all probability, be stable to alkali and certainly stable to detergents. It seems that the loss of chromogenic power is best described as a "covering" of phenolic (and indolyl) groups rather than as a direct reaction with vesicants. The phenomenon of "covering" is usually attributed to the folded character of the protein peptide chains, which may be modified, perhaps through the formation of new hydrogen bonds, by reaction of the vesicant with groups other than those concerned directly in reducing the Folin reagent.

Sulfhydryl groups are of special interest because of their relation to oxidation-reduction reactions which are important in enzyme action and in determining the physical properties of certain proteins. Keratin probably reacts with H through its sulfhydryl groups.[20a,b] In the cases of urease, denatured egg albumin, and papain, sulfhydryl groups disappear under the action of H. Not all the groups in urease react to the same extent, and under some conditions the activity of the enzyme is not impaired as a consequence of the reaction.[5] By working at low phosphate concentration, inactivation can be produced by H or

ethyl β-chloroethyl sulfide. The inactivating action of vesicants is also enhanced at high *p*H values. The phosphate probably protects through competition.[26d] The sensitivities of so-called sulfhydryl enzymes to vesicants vary considerably (see Section 21.3).

21.2.2 Changes in Protein Resulting from Reactions

The changes in properties of proteins resulting from vesicant action have been studied only with material subject to rather drastic treatment. In the case of H, excess liquid vesicant has practically always been present. The necessity of producing experimentally measurable results is the reason for the use of such high concentrations. Perhaps the results may, with caution, be extrapolated to the lower concentrations which are of greater interest.

The proton affinities of a protein are modified by reaction with vesicants. The chief evidences for the participation of the carboxyl and imidazole groups are the changes in the acid-base titration curves and isoelectric points of the proteins.[4,10] In the case of hemoglobin, H also increases oxygen affinity and susceptibility to oxidation to methemoglobin without, however, reacting directly in the "heme" portion of the molecule.[4] After treatment with H, collagen becomes more difficult to gelatinize or to digest enzymatically.[41a,b]

H is a specific hapten in proteins.[36,37] The production of H-protein complexes *in vivo* probably accounts for the sensitization to vesicants (see Chapter 23). Certain products obtained by the reaction of vesicants and serum proteins are said to be toxic to tissue cultures and to whole animals.[22b,c,d]

Nucleoprotein is precipitated by treatment with H to a greater extent than are other proteins.[26a] However, treatment of solutions of nucleoprotein from the thymus or from chicken erythrocyte nuclei in 6 per cent NaCl with low concentrations of H produced no changes in viscosity, nor did the nucleoprotein isolated from H-treated thymus or chicken erythrocyte nuclei show any difference in viscosity from normal material.[13]

21.3 INACTIVATION OF ENZYMES BY MUSTARDS

A very attractive theory concerning the action of vesicants has been the enzyme hypothesis of Peters.[26b p 63] It was based on the finding that *bis*(β-chloroethyl) sulfone (H sulfone) inhibited the oxidation of pyruvate by brain mince, and upon the previously discovered inhibition by H of the respiration and glycolysis of tumor tissue.[26] The use of 2,3-dimercaptopropanol (BAL) as an antidote in arsenical poisoning was developed on the basis of this hypothesis and the evidence that sulfhydryl groups were particularly concerned. The hypothesis proposed that the initial significant lesion produced by a vesicant is the inhibition of an enzyme, and that pathological changes follow as a result of the subsequent changes in metabolism. The enzyme hypothesis was particularized for vesication as a hexokinase hypothesis[37d,e,f] and more generally as a phosphokinase hypothesis.[37j,k] A very similar hypothesis was developed in the open literature with regard not only to vesicants but also to suffocants and lachrymators.[51] The observed actions of the agents (i.e., inhibition of glycolysis, limited response of frog muscle to K^+) are ascribed to enzymatic disturbances brought about by reactions with sulfhydryl groups, in analogy with the action of iodoacetic acid.[49,52] The Peters hypothesis and its success in leading to the development of BAL served as the impetus for testing the actions of vesicants on many enzymes in a more or less pure state, and for the examination of the enzyme contents of the tissues of intoxicated animals.

The action of H on enzymes has been reviewed.[2] In only one or two cases was the rate of inactivation so great as to suggest that the enzyme might compete significantly with the general tissue proteins for the vesicant.[2] The same conclusion seems justified for the nitrogen mustards because, in general, the sensitivities of a series of enzymes fall in the same order for different vesicants. Parallel *in vitro* and *in vivo* studies, particularly of enzymes related to carbohydrate metabolism, show that the sensitivity of an enzyme *in vitro* is not necessarily an indication of sensitivity *in vivo*.[13] Nor does the same enzyme action behave similarly in different tissues of the same animal.[12,21a,b,c,d,f] The profound effects of destruction of cellular architecture on the rates and orientations of metabolic process present an obstacle to study and interpretation of enzyme behavior *in vivo*.[21c] "At the present state of our knowledge it seems doubtful whether further studies of the effects of vesicants on enzymes would aid in the identification of the primary chemical lesion." [13]

Enzymes are proteins. Some may have special prosthetic groups, or active centers, not derived from amino acids. In so far as the enzymes contain the same functional groups as other proteins, their reactions

with vesicants will not differ in kind from those of other proteins. In so far as special groups are present, these may react more or less readily. Reaction of vesicants with groups in an enzyme need not cause inactivation.[8] The sulfhydryl enzymes existing in oxidized and reduced forms are not equally sensitive to vesicants. Some substrates (choline with choline oxidase,[21a,b] glucose with hexokinase [27d]) have a protective action. While these may behave as if they compete for the active center with the vesicant, the protective compound is not able to reverse the action of vesicant after reaction has occurred.

In Table 1 is given a list of the enzymes studied along with estimates of their relative sensitivities. The estimates are necessarily somewhat impressionistic because they are based on reports of experiments in which conditions of treatment varies greatly as to temperature, concentration, and time of action. From the table it is evident that the most sensitive enzymes are among those concerned with choline (choline and betaine aldehyde oxidases and brain cholinesterases), with carbohydrate and phosphate metabolism (hexokinase, creatine phosphokinase, pyrophosphatase, and pyruvic oxidase), and with protein (peptidases of serum, plasma, skin, and lung). There is no evidence that these *in vitro* inactivations are produced by as mild treatments as have definite inhibitory effects on cell division or on the swelling phenomenon described in the following sections.

21.4 YEAST METABOLISM AND REPRODUCTION

β-Chloroethyl vesicants interfere with the metabolism and reproduction of yeasts. The development of colonies in plate cultures of treated yeast has been used to demonstrate lethality,[12,20jj,nn,40,48] and the growth in fluid media measured by turbidimetric means has been used to demonstrate effects on growth rate.[20l] The presence of dead cells, unless corrected for, may produce errors in turbidimetric growth rate methods, and slowing of growth may be sufficient to prevent colony formation in plating-out methods.[20nn] No serious discrepancies exist in the findings by the two methods, although the turbidimetric method seems to yield more information.

A single treatment with a sublethal dose of H prolongs the generation time of yeasts for as many as ten generations. Growth follows the usual logarithmic formula during this time and the period of subnormal growth rate is terminated by cessation of growth for a period followed by return to the normal untreated rate.[20l] The inhibition caused by H, HN2, HN3, or ultraviolet light is irreversible, but the inhibition caused by formaldehyde, iodoacetate, cyanide, fluoride,[23a] or divinyl sulfone [23e] is reversed by suspension in fresh media. Divinyl sulfone seems to have both reversible and irreversible effects.[20ss] Inhibition by divinyl sulfone is lifted by changing *p*H from 7 to 5.5, or by adding glutathione to the poisoned yeast,[20p,q] although the divinyl sulfone bound by the yeast is not liberated.[20bb] The role of glutathione is obscure. Although sulfhydryl groups disappear from yeasts treated with H or divinyl sulfone, the amount disappearing is not proportional to the effect on reproduction; nor are the sulfhydryl groups restored to normal by resuspension or changing *p*H,[20bb] conditions which at least partially reverse the inhibition by divinyl sulfone.[23e] The possibility of reversing the effects of H by oxidizing combined H to sulfone *in situ* has been considered, but the toxicity of the peracids required proved too great.[23b,t]

Morphological abnormalities appear in H-treated yeast after 10 hours, but after 25 hours the cultures are composed of normal appearing cells. Probably the return of normal growth rates depends on repeated divisions of a few cells which escape injury.[20ee] The permeability of yeast to chloride, thiosulfate, and phosphate is not affected by treatment with H.[20ee] About half of the H reacting with yeast is in a form soluble in trichloroacetic acid. The remainder is fixed in part by water-soluble protein and in part by insoluble cell constituents.[20ss]

The reproductive defect has no simple relationship to the gross metabolism of the yeast. Much lower concentrations of vesicants inhibit growth than have any effect on either oxygen consumption or anaerobic carbon dioxide production,[12,17b,20v,40] or on the usually poison-susceptible utilization of acetate.[20dd] Yeast enzymes both *in vivo* and *in vitro* are much less sensitive than is the reproductive system.[18] There are at least two, if not many more, H-sensitive systems connected with reproduction, as is shown by the linear relationship between amount of H fixed by yeast and concentration during treatment [20y,z] and by the lack of a similar regularity between H concentration and prolongation of generation time. Abrupt changes in slope occur in the latter relationship.[20u,y] The actions of reversible poisons are generally additive to the action of H, indicating that a multiplicity of functional disturbances can result in prolongation of gen-

TABLE 1. Sensitivities of enzymes to vesicants *in vitro*.

Standard treatment is considered to be incubation with 3 mM H or equally active amounts of other reagents for ½ to 1 hour.

0 no effect
1 up to 20% inactivation
2 20–60% inactivation
3 60–90% inactivation
4 90–100% inactivation

H *bis*(β-Chloroethyl) sulfide
HN2 Methyl-*bis*(β-chloroethyl)amine
HN3 *tris*(β-Chloroethyl)amine

Enzyme	H	HN2	HN3	References
Adenosine deaminase	0	..	..	21b
Adenylic acid deaminase	2	2	..	13
Adenylpyrophosphatase	2	2	..	13
Adenylpyrophosphatase (myosin)	..	1	1	21b
Aerobic phosphorylase	2	2	..	13
Alanine oxidase	..	activity increased	..	21b
Alcohol dehydrogenase	1	..	..	37e
d-Amino acid oxidase	0–1	1	0	6, 37e
Aminopeptidase	0	..	..	3
Amylase	0	..	..	37e
Arginase	..	0	0	21b
Ascorbic acid oxidase	0	..	..	6
Betaine aldehyde oxidase	..	4	4	21b
Carbonic anhydrase	0	0	0	37e
Carboxylase	0	1	1	6, 21b, 37e
Carboxypeptidase	0	..	..	3
Catalase	0	..	..	37e
Cathepsin	1	..	..	37e
Cholinesterase (serum)	0	2	2	6,19d,21a, b,36k
Cholinesterase (brain)	..	3	4	21b, 36e, 37p
Cholinesterase (kidney)	..	1	..	13
Cholinesterase (eye)	..	1	..	19d
Choline oxidase	4	4	4	13, 21a,b
Chymopapain	1	..	..	3
Chymotrypsin	1	..	..	10
Creatine phosphokinase	4	3	..	13
Cytochrome oxidase	0	0	0	6, 21b, 37e
Deuterohexokinase	2	2	..	13, 37j
Diaphorase	0	..	..	37e
Enolase	0	..	..	13
Fumarase	0	..	..	37e
Glucose dehydrogenase	1	..	..	37e
Glutamic acid oxidase	..	2	2	21a,b
Glyceraldehydephosphokinase	-	..	..	13
α-Glycerophosphate dehydrogenase	0	..	..	37e
Glyoxalase	0	..	..	37e
Hexokinase	4	2	..	10, 13, 37d, h, i, j, k, o,p
Histaminase	3	0	0	6, 21b
Hyaluronidase	0	..	..	41e
Laccase	0	..	..	37e
Lactic acid dehydrogenase	0	..	..	6, 21b, 36m, 37e
Lanthionase	0	..	..	12
Leucine deaminase	..	..	1	21b
Malic acid dehydrogenase	0	..	1	36f, 37e
Myokinase	0	..	..	13, 21b
Papain	2	0–1	..	3, 8, 37e,p
Pepsin	0–3	1	1	10, 21b, 37e
Pepsinase (beef spleen)	0	..	..	3
Pepsinase (swine kidney)	2	..	..	3
Pepsinogen	2	..	..	10
Peptidase (serum, plasma, skin, lung)	4	4	..	3, 7
Peroxidase	0	..	..	37e
Phenylalanine deam'nase	..	1	1	21a,b
Phosphatase (acid and alkaline)	0	1	2	19r, 21b, 47
Phosphohexokinase	0	0	..	13
Phosphoglucomutase	0	0	..	13
Phosphorylase	2	1	1	13, 21b
Polyphenoloxidase	0	0	0	21b, 37e
Ptyalin	0	..	..	37e
Pyrophosphatase	3	3	..	13
Pyruvate phosphokinase	2	2	..	13, 37j
Pyruvic oxidase (*B. Coli*)	3	..	..	6, 37b,e,j
Pyruvic oxidase (brain)	3	1	..	36b,e,f
Pyruvic oxidase (kidney)	..	3	3	21a,b
Pyruvic oxidase (liver)	..	..	2	21a,b
Pyruvic oxidase (skin)	3	..	..	36d
Ribonuclease	0	..	..	17a
Succinodehydrogenase	0	2	2	6, 21b, 36f, 37e,p
Sucrase	0–1	..	..	10, 37e
Thymonucleodepolymerase	..	0	..	13
Triosephosphate dehydrogenase	0	2	..	6, 37p
Trypsin	0	2	..	7, 37e
Trypsinase	0	..	..	3
Urease	0–2*	..	..	8, 20ii, mm, 37e
Uricase	..	..	2	21b
Valine deaminase	..	0	1	21b
Xanthine oxidase	0	..	..	6, 37e
Zymohexase	0	..	..	37e

* Result depends on phosphate concentration.

eration time.[20a] The action of vesicants on yeast is "very complex" [40] and lethality is probably related to the accumulation of many small defects.[20ii]

Separate drastic H treatments of the vitamins necessary for yeast growth fail to make them unavailable for yeast. This applies to biotin, inositol, thiamine, pyridoxine, and β-alanine.[12] The following water-soluble constituents of yeast extracts are not affected by H treatment of yeast:[20y] adenosine triphosphate, diphosphonucleotide, adenylic acid, and nicotinic acid.

Other vesicants and related compounds that are

lethal to yeast are HN3,[40] HN2,[2a,b] and benzyl and ethyl β-chloroethyl sulfides.[12]

21.5 CORNEAL METABOLISM AND LOOSENING

Exposure of the isolated cornea to saturated H vapor (which produces severe delayed injury in rabbits after a 1-minute exposure) results in loosening of the corneal epithelium. The loosening can be quantitatively measured after 5–12 hours.[19f] At 28–33 C° the process of loosening takes 6 hours to develop. The loosening does not develop if the treated cornea is kept at 0–18 C° after the fourth hour. After 10–12 hours at low temperature, re-exposure to 28 C° often results in loosening.[19a] Anaerobiosis also inhibits loosening. Anaerobiosis during 10 hours after exposure partly inhibits loosening in the subsequent 10 hours of aerobiosis.[19a] The dependence of loosening on deranged metabolic processes is indicated by these findings. Physical loosening of the Danielli type is produced by treatment with alcohols, but is immediate.[19a] Delayed loosening is characteristic of vesicants, freezing, iodoacetate, fluoride, and certain drugs, especially histamine.[19j] That proteolysis is concerned is indicated by the ability of trypsin and chymotrypsin, when properly injected, to produce the loosening. Ribonuclease, lipase, and hyaluronidase have no comparable effect.

Treatment of cornea with H results in increasing affinity for acid dyes, probably because of formation of sulfonium groups.[19c]

Many substances injected into the cornea produce clinical lesions. A survey (not including vesicants) of these and others tends to dissociate the effects on isolated enzymes from lesion production. Some which have no effect on corneal metabolism produce lesions, some which affect isolated enzymes of the cornea do not affect the same enzymes *in vivo*, and some which affect respiration or glycolysis of surviving cornea produce no lesions when injected into the cornea *in situ*.[19a]

Exposure of supravitally maintained beef corneas to H vapor produced a 30 per cent drop in oxygen consumption, which becomes apparent 10 hours after exposure. Increase of exposure beyond a moderate dose produces no greater change. The rate of disappearance of lactic acid decreases immediately after exposure, but inhibition of anaerobic glycolysis develops only after long exposures and long incubation times. The threshold for severe clinical symptoms in the rabbit eye is 1 per cent of that for inhibition of glycolysis in the surviving beef eye. Thus, inhibition of anaerobic glycolysis appears to bear no causal relation to the development of clinical symptoms.[19b] The increase of lactic acid in corneas exposed to H is due to an increased rate of its production in H-exposed corneal epithelium and can be inhibited by iodoacetate. The major portion of normal, metabolized corneal carbohydrate does not pass through lactic acid phase of the carbohydrate cycle.[19e] Glycogen and phosphate fractions are but slightly affected by exposure to H.[19a] The cornea utilizes pentoses, particularly ribose and xylose, at about half the rate that it uses glucose. Addition of ribose spares glycogen and lactate, and its utilization is inhibited by iodoacetate and fluoride but not by arsenite or malonate. Exposure of cornea to saturated H vapor for 10 minutes has no effect on ribose utilization. Only slight inhibition follows 20-minute exposures.[19i] Pyruvate is used more rapidly than any other tested substance by cornea, but exposure to H does not effect this utilization. The reaction, which is not a simple decarboxylation, occurs in the epithelium and not in the corneal stroma.[19i] Among products which might result from pyruvate, acetate and butyrate are used only slowly, but acetoin is used rapidly. H does not inhibit acetoin utilization, but does inhibit butyrate utilization.[19a]

Exposure to H increases the nonprotein nitrogen content of beef corneas. One-half to two-thirds of the increase is in the form of amino nitrogen.[19a] A 15-minute exposure produces a maximal effect which, however, is not evident until after a latency of 3–6 hours. The increase is independent of temperature from 28–35 C°, but is only one-half as great at 13–18 C°.[19a] The rate of disappearance of ammonia is not affected by H.[19a] The increased nonprotein nitrogen probably results from proteolysis.[19a]

21.6 TISSUE CULTURES

The effects of H and various other compounds on tissue cultures depend on the dosage. Large doses produce coagulation of cells, probably because of acid production.[32a] The general reaction to H or HN2 involves shrinkage of cells, withdrawal of fine processes, swelling of fat globules, and nuclear shrinkage.[32] Smaller doses inhibit growth.[32a] Products from the action of H or HN2 on fowl plasma are toxic to tissue cultures and inhibit wound healing in mice.[32b,c,d] The products are less toxic than the vesicant from which

they are formed, but it seems unlikely that the toxicity is due to residual vesicant since it is not removed by hot acetone extraction of the dried powder. Neither thiodiglycol nor HCl produces similar products from plasma.[20d] HN2 inhibits the growth of chick embryo heart cultures and, at lower concentrations, the peristaltic movements of gut fragments. The toxicity decreases during incubation. There is no differential susceptibility between epithelium and fibroblasts. The first observable changes are in mitochondria.[29] Bone marrow cultures from H-poisoned animals show abnormalities chiefly in the leucocytes and their mobile precursors.[21] Cultures of normal bone marrow can be used to demonstrate protective action against H by various compounds.[22]

21.7 CARCINOGENESIS

The induction of tumors in mice by carcinogenic hydrocarbons is inhibited by H[23] through a local and nonpersistent action. That is, H and the hydrocarbon must be applied together to demonstrate inhibition. The epithelial hyperplasia preliminary to tumors is not affected.[24] Among other compounds, H sulfone possesses the same ability to a lesser degree, but H sulfoxide does not possess it at all.[25] The anaerobic glycolysis of tumor mince is inhibited to a greater extent by H than is its respiration.[26] The observations indicate to the writer that inhibition of mitosis may be the cause of the prevention of development of tumors.

21.8 PERMEABILITY

The permeabilities of erythrocytes,[18] of yeast,[20c] and of the cornea[20a] are but little, if at all, affected by H. In *Nitella* treated with 2 or 3 millimoles of H permeability is increased and turgor drops. The change is rapid and is not produced by the hydrolytic products of H.[11] Corneal turgescence is reduced by the action of H[20a] *in vitro*[20b,d] and *in vivo*.[20c] Since the water content of corneal epithelium is modified by substances and treatments which do not cause epithelial loosening, the two are not causally related.[19a] The presence of a capillary permeability factor (leucotaxine) in H blister and lung edema fluid (phosgene produced) indicates that this substance is liberated by tissues subjected to the action of chemical warfare agents. Its relation to the primary events remains obscure.[32]

The transformation of the shape of rabbit erythrocytes from disc to sphere, which is produced by external pressure and is perhaps related to permeability, is not modified by treatment with HN2.[18]

21.9 EFFECTS ON NUCLEI AND NUCLEAR ACTIVITIES

Chromosomal Mechanisms

The effects of H on chromosomal mechanisms have been studied with *Drosophila melanogaster* and with *Tradescantia bracteata*. Sublethal doses in drosophila reduce fertility by interference with meiosis and embryogenesis. The rate at which sex-linked lethals appear is much increased over normal. Many chromosomal breaks and rearrangements appear.[32a] A similar situation (with chromosomal breaks and fragmentation) is found in H-treated pollen grain nuclei of *T. bracteata*. Severe effects are nuclear pyenosis and cell death. Surviving cells can divide and transmit chromosome abnormalities.[32b]

Mitosis in Mammalian Cells

In corneal epithelium, a small fraction (about 1 per cent) of the cells can be observed to be in mitosis at any given time. Application of H or HN2 diminishes the number in mitosis greatly. The delay is in the onset of mitosis. Those cells which have begun the process (i.e., show a mitotic figure) pass through to division without delay. The doses required to produce this effect by direct application are much smaller (i.e., about 1/100) than those which suffice to cause clinical damage. Parenteral injection of HN2 sufficient to produce delayed death inhibits mitosis in intestinal mucosa and bone marrow, as well as in corneal epithelium. Recovery in the cornea occurs spontaneously after a slow development of maximum inhibition many hours after dosage at threshold levels.[19a] In spite of the inhibition of mitosis, healing of mechanically or vesicant-denuded areas of cornea occurs normally up to the time that the epithelium sloughs off. This healing takes place by migration of marginal cells, a process not inhibited by vesicants but inhibited by anoxia, iodoacetate, local anesthetics, epinephrine, etc.[19a] The effective doses for mitotic inhibition in cornea are far below the necrotizing doses for H, HN2, and HN3, and at about the necrotizing dose for lewisite.[19b] Higher doses than those which inhibit mitosis produce nuclear fragmentation in corneal epithelium. The fragmentation is considered a form of pathological mitosis resulting from action of the vesicants on cells in a "premitotic" state.[19c] At any rate, those changes in the en-

vironment such as reduced temperature and anoxia which inhibit mitosis in normal cornea inhibit the development of nuclear fragmentation in vesicant-treated cornea.[19w] In regenerating liver, where mitosis is active and inhibited by H,[18] nuclear fragmentation does not seem to result from vesicant treatment, indicating that the sequence of events in corneal epithelium is not general.[19v]

Mitosis in Marine Eggs

The development of starfish eggs is inhibited by H in sea water.[49] The effects of vesicants on mitosis have been studied in detail, using *Arbacia punctulata* eggs.[14] The observed effects depend on concentration, length of contact, and the time during the developmental routine at which contact occurs with vesicants. When suitably treated with vesicant before fertilisation, delay occurs during the events occupying the period between 55 and 75 per cent of the normal cleavage time (early prophase). This may correspond to the "premitotic" state in corneal epithelium. The eggs reach the "streak" stage in the same time, whether treated or not, and pass from spindle stage to cleavage independently of dosing. The intervening time (streak to spindle) may be prolonged eightfold. If the vesicant is applied for a limited period after fertilization, the delay in the first cleavage can be produced only by treatment before 55 per cent of normal first cleavage time has elapsed, and is progressively less the closer to the time of cleavage as the treatment is applied. Application between 55 per cent of normal first cleavage time and 75 per cent of first cleavage time produces maximum delay in the second cleavage. Treatment at progressively later times between early prophase I and early prophase II produces less and less inhibition, until the second cleavage is not delayed by treatment at or after the latter time. The system behaves as if a sensitive substance more or less specific to each cleavage had been variously protected or exposed to the vesicant during the development. The sensitive substance is not restored by resting before insemination and after treatment.[14]

Effectiveness in the reaction is greatest for HN3 and progressively less for H, HN2, and formaldehyde. Formaldehyde is effective over a very narrow range, about 1–2 millimoles. Greater concentrations produce granulations and blistering of the cells after about 2 hours. Abnormalities in divisions are evident in eggs treated more heavily than required for the above demonstrations, or when the development proceeds in the presence of vesicant. Treatment of sperm has not been studied to so great an extent as the treatment of eggs. However, many abnormalities result when normal eggs are brought into contact with treated sperm. Such sperm may enter eggs and, although they do not initiate the rise of a fertilization membrane, nevertheless prevent the entrance of more virile sperm which actively swarm about the eggs.[14]

As a result of treatment of arbacia eggs, the nuclei exhibit a three-fold increase in volume and abnormalities of development can be observed in stained sections.[14]

Swelling Phenomena

The nucleated ghosts prepared by saponin hemolysis of avian erythrocytes swell when placed in 6 per cent NaCl or in 0.1 per cent sodium dioctylsuccinosulfate (Aerosol OT) in 0.9 per cent NaCl. These materials are solvents for nucleoprotein, but do not free it from the nucleated ghosts. The swelling of ghosts in Aerosol OT solutions is enormous (i.e., several hundredfold) but definitely limited. The mechanism of the swelling phenomenon is believed to be osmotic and dependent on the solubility of the normally undissolved[62] nucleoprotein in solutions of Aerosol OT and in 6 per cent NaCl. It is believed that solvent action on the nucleoprotein enhances the osmotic pressure of the nuclear contents and fluid is drawn into the nuclei which consequently swell until the hydrostatic pressure produced by the elastic resistance of the membrane balances the osmotic pressure.[18]

The effect of treatment with vesicants is to decrease the swelling. On the above hypothesis, the vesicant either reduces the osmotic effect of the nucleoprotein or increases the rigidity of the elastic container. No effect indicating aggregation can be observed in the case of isolated nucleoprotein treated with H at the low concentrations necessary to inhibit swelling of the ghosts. The second hypothesis is, therefore, the more probable. After reaction with vesicant has occurred, the inhibition of swelling is not reversible by resuspension or by treatment with thiosulfate. The inhibition requires time and its rate can be measured. It is accelerated at increased temperatures. The sensitivity to vesicants of the swelling phenomenon is greater than that of any other isolated manifestation of vesicant action.[18]

Intact erythrocytes are swollen and hemolyzed by Aerosol OT. The swelling is less sensitive to inhibition by vesicants: 86 per cent swelling loss is pro-

duced when 870×10^{-11} millimole of HN2 has reacted per erythrocyte and when 7×10^{-11} millimole has reacted per ghost; the corresponding figures for 70 per cent loss are 360×10^{-11} and 1×10^{-11} millimole. The difference must be ascribed chiefly to the reaction with hemoglobin which is present in the intact cell but not in the ghost. The hemoglobin could properly be called the more reactive substance in the intact cell, but it is not important to the swelling phenomenon.[15]

Among substances which are not vesicants, cyanide, iodoacetate, and fluoride ions have no effect; formaldehyde is effective in quite low concentrations (i.e., of the same order of magnitude as the vesicants). The damage by formaldehyde is less the greater the concentration of nucleated ghosts, whereas with H, HN2, and HN3 the amount of damage is independent of the ghost concentration.[15]

Suspensions of lung, bone marrow, kidney, spleen, intestinal mucosa, and skin of rats and rabbits are swollen by Aerosol OT. The concentration of Aerosol OT required to produce maximum swelling is different for each tissue. In some cases (i.e., intestinal mucosa) the swelling ability is rapidly lost after preparation, whereas in others the capacity to swell is retained long enough to demonstrate that the tissues are sensitive to vesicants. For lung and bone marrow, the sensitivity is of the same order as for ghosts. In spite of the sensitivity of the isolated tissues, no decrease in swelling ability of the lung or bone marrow after LD_{50} or supra LD_{50} doses of HN2 or HN3 to rats or rabbits could be demonstrated up to 4 or 5 hours after dosage. Various possibilities are considered in explanation, but the problem of the key lesion in vesicant injuries is not solved by the swelling phenomenon.[15]

Chapter 22

SYSTEMIC PHARMACOLOGY AND PATHOLOGY OF SULFUR AND NITROGEN MUSTARDS

By *William P. Anslow* and *C. Riley Houck*

22.1 INTRODUCTION

This chapter is a review of classified literature concerning the systemic pharmacologic and pathologic actions of the sulfur and nitrogen mustards (β-chloroethyl vesicants). Attention is given chiefly to *bis*(β-chloroethyl) sulfide (H), ethyl-*bis*(β-chloroethyl)amine (HN1), methyl-*bis*(β-chloroethyl)-amine (HN2), *tris*(β-chloroethyl)amine (HN3), and isopropyl-*bis*(β-chloroethyl)amine (TL 301). Data are included on additional compounds deemed pertinent to the understanding of the action of the above compounds.

Systemic injury by the β-chloroethyl vesicants is that injury which results from distribution of the agents by way of the circulation. Thus, systemic injury always follows parenteral administration, including skin application. In addition, it arises from oral administration. However, on inhalation, the development of systemic injury varies with the species, apparently depending on their size. In smaller animals in which the narrow upper respiratory passages may absorb the vapor, systemic injury results only when the animals do not succumb to asphyxial death (edema of the glottis). In larger animals, including man, systemic injury following inhalation is rarely demonstrable. Here, the wider respiratory passages permit vapor to reach the lungs where damage resulting in extensive edema may precipitate rapid asphyxial death. If rapid death is avoided, superimposed secondary infection may be the cause of delayed death in the absence of significant systemic injury. In this chapter inhalation is discussed only when it has involved systemic absorption.

22.1.1 Common Features of Systemic Effects

Many features of systemic intoxication are common to the β-chloroethyl vesicants. Following administration of LD_{50} doses, animals show no immediate injury but die of systemic intoxication in 70-140 hours (delayed death), and pathologic examination of such animals reveals injury to the same tissues, differences being recorded only in the intensity of the lesions. Therapeutic approaches to alleviation of systemic intoxication have attained no significant success, although some prophylactic procedures will prevent systemic injury. Systemic injury in man following inhalation or skin exposure is infrequent and is a bad prognostic sign.

In small animals given doses causing delayed deaths, no toxic effects may be evident up to 40 hours, but the animal soon stops eating and drinking and rapidly loses weight. Muscular weakness and debilitation increase progressively until the animal is prostrate. Watery diarrhea appears, reflecting damage to the intestinal tract; there is a loss of control of body temperature, slowing and enfeeblement of respiration, and exodus may be preceded by convulsive tremors which probably reflect cerebral anoxia.

In the dog, nausea and vomiting accompanied by anorexia usually begin a few hours after intoxication and may persist with increasing severity through the second or third day, and diarrhea variably stained with blood makes its appearance by the second or third day. From the third to the fifth day, weakness appears, body temperature is reduced, the extremities become cold, and the animal gradually goes into terminal coma. Death usually results from respiratory failure which in turn is a consequence of peripheral circulatory failure.

The evidence for the existence of peripheral circulatory failure consists of reduction in the volume of extracellular fluid, circulating plasma volume, total circulating red cell volume, total circulating plasma protein, and plasma chloride. Terminally there is a marked oxygen unsaturation of the jugular blood (arterial saturation presumably being normal). Alleviation of some of the above changes by fluid and electrolyte replacement at terminal stages causes dramatic improvement. As this therapy fails to correct underlying lesions, only transient benefit is achieved.

Changes in some blood constituents, e.g., glucose, lactate, and pyruvate, are inconsistent and lack specificity, since they are associated with unrelated

disorders or experimental procedures. Changes in other blood constituents, e.g., albumin and globulin, nonprotein nitrogen, fibrinogen, inorganic phosphate, pentose, phosphocreatine, cholesterol, and other lipids, are more consistent. Such changes appear to possess some uniformity, since they are associated with a limited number of related traumatic procedures. In some cases, they are concomitants of peripheral circulatory failure; in others, of infectious diseases, metabolic disorders, burns, etc. They possibly reflect some underlying functional disorder common to these various forms of injury.

The β-chloroethyl vesicants are cytotoxic agents capable, if present in sufficient concentrations, of killing any type of cell. However, when distributed in the body in the small amounts which are present after LD_{50} doses, the most sensitive tissues are the blood-forming organs (bone marrow and lymphoid tissue) and the intestinal mucosa. Bone-marrow injury consists of depletion of the granulocytic series and degenerative changes in the megakaryocytes, and culminates in aplasia. Lymphatic tissue injury in the spleen consists of fragmentation of lymphoid cells with phagocytosis of chromatin particles, and cellular depletion of the sinuses. In the thymus, cytolysis of the lymphoid cells of the thymic corpuscle and interstitial tissue occurs. Injury to the intestinal tract, particularly the small intestine, consists of destruction of the mucosa with desquamation and necrosis of the epithelium, and hemorrhage in extreme cases.

Injury to the blood-forming organs is reflected in changes in the circulating blood. The abrupt injury to the lymphatic tissue is paralleled by an early disappearance of lymphocytes from the blood. At the same time there is an absolute granulocytosis, the result of stimulation of the bone marrow, leading to the discharge of granulocytes into the circulation. This stimulating process may be completed at 24 hours, so that blood counts at 24-hour intervals frequently show only a progressive leucopenia which reaches a maximum *pari passu* with other symptoms at 3 or 4 days.

In surviving animals extramedullary hematopoiesis may occur in the liver before regeneration occurs in the bone marrow and lymphoid tissue. Lymphocytes recover before granulocytes, and marked hyperplasia of the thymus and lymph nodes, parallel with this recovery, is histologically demonstrable. Regenerative activity in the bone marrow may cause a discharge of immature granulocytes sufficient to raise abruptly the leucocyte count in the blood. Regenerative activity may persist for weeks.

The only prophylactic and therapeutic procedures which have attained any degree of success are those operating on the principle of internal decontamination. Various substances (e.g., sodium thiosulfate and hexamethylenetetramine) which are known to react chemically with the β-chloroethyl vesicants significantly alter mortality rate when given prophylactically in doses sufficient to yield relatively high blood levels. The same substances are effective therapeutically after skin contamination if treatment is initiated rapidly, i.e., before significant systemic absorption occurs. It seems apparent that these procedures effectively decontaminate the agents in the blood and extracellular fluids and thus prevent entrance of the agents into the cell. Once a sufficient quantity of a β-chloroethyl vesicant has reacted with cells of the body, the damage is irreparable so far as existing knowledge goes. Thus all attempts at specific therapy, as well as of symptomatic therapy, have failed.

In man there are few uncomplicated data indicating systemic injury. Early vomiting, by some associated with systemic absorption, is believed to be nonspecific because it occurs in a variety of conditions involving skin trauma. Delayed gastrointestinal disturbances and leucopenia have in many cases indicated systemic intoxication. The frequency and prolonged duration of the gastrointestinal disturbances possibly indicate an increased sensitivity of the human intestine to the action of the β-chloroethyl vesicants. On the other hand, the human hematopoietic system seems relatively insensitive, as judged by the rare appearance of leucopenia, usually present only in fatal cases.

22.1.2 Individual Pharmacologic Actions

Above LD_{50} doses, and sometimes at LD_{50} doses, certain characteristic pharmacologic actions are manifest, chiefly on the nervous system. They are readily elicited on intravenous administration, less readily on administration by other routes.

Cholinergic action is possessed by both H and HN2, and is characterized by muscarinic action on glands and smooth muscle and nicotinic action on autonomic ganglia and skeletal muscle. In the case of both agents, peripheral stimulation of local effector cells appears to account for the muscarinic responses, although central excitation, apparently minimal, cannot be excluded. Cholinergic action is not considered a factor in the development of the syndrome

leading to delayed death and is not responsible for late vomiting and diarrhea. Cholinesterase inactivation is probably not involved in this cholinergic action.

Parasympathicolytic action is shown by HN3 at small doses, as judged by paralysis of cardiac vagal fibers and antagonism of the action of parasympathomimetic drugs. A similar parasympathicolytic action of H, HN2, and TL 301 appears to be present in severe intoxication.

Convulsive action is so distinctive of HN3 as to warrant classification of this agent as a true convulsive drug. High doses of this compound given parenterally have an immediate, direct, intense convulsive action which results in death within 6 hours. Central stimulation is a property of H and HN2 at high doses, but the action is not similar to that of HN3.

Paralytic action is possessed by both HN2 and HN3. This action is characterized by a progressive, irreversible muscular weakness and may cause death in a number of hours.

Neurologic injury has been observed in animals intoxicated with HN1 and HN2 by either gassing or intravenous administration, but never after intoxication by other routes or with other agents. This injury has usually appeared about the third or fourth day in animals showing no other evidence of systemic intoxication. In extreme cases the injury is fatal, and among survivors hyperirritability persists for weeks.

22.2 (β-CHLOROETHYL) SULFIDE (MUSTARD, H, DH, DHX)

22.2.1 Pharmacology

Toxicity

The parenteral toxicity of H for various species is shown in Table 1. For additional information on the toxicity of H, the reader is referred to the following: intraperitoneal administration to the mouse,[17b,21] rat,[17a] and dog;[18a] oral administration to the rabbit;[16b,21] intramuscular administration to the rabbit;[124] and application of neat H to the unclipped fur of the goat and rabbit.[18]

Distribution and Excretion of H

H penetrates the skin readily (see Chapter 23). A large part of that which has penetrated passes through the skin, into the circulation, and becomes available for producing systemic injury.[9] Thus extirpation of the contaminated skin of rabbits[49] and rats[122d] is efficacious in prevention of systemic injury and in saving the animals only if the procedure is carried out within 10–15 minutes after contamination. Having entered the blood, H is rapidly distributed to the tissues. Fifteen minutes after skin application of H containing S^{35} the radioactive sulfur has been found in all examined tissues except the eye.[122a] Following the application of 5 mg of radioactive H to the skin of the rat, 0.17 mg was distributed throughout the organism within 30 minutes. This amount is more than an LD_{50} dose given intravenously.[122d]

Under conditions which permitted tracing an average of 85 per cent of the S^{35} applied to the skin of rats as H, the concentration of S^{35} in the tissues reached maximum values between 2–6 hours and thereafter decreased until fairly steady values were reached at 24–72 hours.[122a] At all times the concentration in any one tissue was found to correspond closely to the average concentration in all tissues, except in the kidney which consistently showed higher concentrations. A concentration of S^{35} significantly higher in the bone marrow than in lung, liver, kidney, and brain has been reported[26b] to follow skin contamination with radioactive H. However, this important observation has not been confirmed in other laboratories.[16d,e,122a] In the blood the concentration rose during the first 6 hours and fell thereafter until a secondary increase, possibly related to hemoconcentration, occurred at 48 and 72 hours.[122a] During the first 6 hours the concentration of S^{35} in the plasma was higher than in the cells, but at 12 hours and thereafter the situation was reversed. The total urinary excretion in 72 hours contained 50 per cent of the applied S^{35}, the greatest fraction having appeared in the first 24 hours.[122a] The excreted product was in the neutral sulfur fraction of the urine.[122a]

When a solution of radioactive H dissolved in triacetin was injected intravenously, S^{35} was found in the urine[16a] and bile[16a] within 10 minutes. Urinary excretion paralleled urine formation. At termination of the longest experiment (7 hours) the S^{35} concentration in the urines was still high. The highest total excretion was obtained in one experiment of 4 hours' duration and amounted to 22 per cent of the S^{35} injected. In the bile 7 per cent of the injected S^{35} was excreted within 3 hours; the maximum concentration occurred between 20 and 30 minutes. The excreted product was not identified. At the end of the experiment (3¼ hours), the contents of the stomach and small intestine contained relatively small quantities

TABLE 1. Parenteral toxicity of H for various species. (LD_{50} in mg/kg).

PG = propylene glycol ca. = approximately ing. = ingestion
TG = thiodiglycol inj. = injection or injected neat = undiluted

Route	Intravenous				Subcutaneous				Cutaneous		
Animal	LD_{50}	Ref.	Solvent	Remarks	LD_{50}	Ref.	Solvent	Remarks	LD_{50}	Ref.	Remarks
Mouse	8.6	23n	PG	0.05 ml soln per 20 g mouse	26	23n	PG	0.1 ml/20 g	92	23k	
					30	21	Neat				
					20 to 30	84	Tributyrin				
Rat	0.7	23n	PG	0.1 ml/200 g	3.2	23o	PG	1 ml/200 g inj. in flank	ca. 18	23k	Site, back; ing. prevented
	3.3	23o	Neat								
					9.0	23n	PG	0.5 ml/200 g inj. in flank	20	17b	†
									11	123a	‡
									5–6	65	Possible ing.
					7.4	23o	Sesame oil	1 ml/200 g inj. in flank	>168	37	Site, tail§
					5.0	23p	Sesame oil	1 ml/200 g inj. in back			
					8.5	23p	95% alcohol	1 ml/200 g inj. in back			
					5.2	23o	Neat	Flank			
					2–5	84	Tributyrin	Vol. and site not stated			
					1.6*	123a		0.2% soln			
Rabbit	2.7	23o	PG	0.5 ml/kg	20–30	84	Tributyrin		ca. 100	23k	Ing. prevented
	ca. 1.1	23p	TG	0.5 ml/kg					40–50¶	116	Ing. prevented
	3.6	23o	Neat	Rapid inj.							
	4.5	23o	Neat	Slow inj.					10–15‖	104n	
	5–10‖	104n									
Guinea pig					?20–40	84	Tributyrin		20–25	65	
Dog	0.2	30f	TG	In a vol. of 1–2 ml	5–10‖	104n			20	65	
	1–2**	104n									
Goat					40	84	Neat		50	65	

* The value 1.6 mg/kg is given for H dissolved in sesame oil, but the toxicity of H in corn oil or in liquid paraffin was found to be similar.

† To prevent excessive evaporation, the site was covered for 15 minutes at which time decontamination by scrubbing with ether was carried out.

‡ The animals were anesthetized during the application and kept so until the agent was no longer visible on the skin.

§ Earlier [23n] the LD_{50} for H applied to the tail of rats was reported as 14 mg/kg. With ingestion prevented,[37] 1 of 4 rats died of unknown causes following application of 168 mg/kg of H to the tail.

‖ The value is stated to be "minimum fatal dose." No details are given.

¶ This value amends an earlier value, 10–15 mg/kg,[104n] but the amended value remains lower than the American value.

of S^{35} which must have been excreted into the gut by some route other than the bile.

The kidney, liver, and bone marrow showed an S^{35} content higher at one hour than at 2½, 4, and 12 hours, whereas the peak concentration in the lung occurred at 4 hours. The concentration in bone marrow and intestine at 1 hour was comparable to that in the liver, but remained lower than that in the kidney and lung.[106d,e,h] At 1 hour only a very small quantity of S^{35} was found in the thyroid, heart muscle, skin, hair, and in a representative sample of skeletal muscle.[106h]

At 1 hour the distribution ratio of S^{35} between cells and plasma (concentration in cells concentration in plasma) was 0.38, and the total quantity of S^{35} in the cells and plasma was 10 per cent of that originally injected. The concentration in the cells remained approximately constant. However, the concentration in the plasma decreased until at 4 hours the above distribution ratio rose to 0.54. After 4 hours the plasma concentration remained fairly constant. When a solution of radioactive H in triacetin was added to whole blood *in vitro*, the distribution ratio at 12 hours was nearly the same as that at 12 hours *in vivo*. However, in the early stages (20 minutes) *in vitro*, the concentration of S^{35} was higher in the cells than in the plasma, a circumstance which gave a distribution ratio of 1.7.[106d,e] A considerable portion of the S^{35} (mainly in the plasma) was extractable by means of ether and acetone.[106h]

Gross Clinical Observations

The systemic action of H in experimental animals and man has recently been reviewed.[8,11] When given to most laboratory animals parenterally, H in supra-LD_{50} doses can cause salivation, vomiting, defecation, bradycardia, and arrhythmia followed by tachycardia, increased respiratory rate, vagal paralysis and partial heart block, psychomotor restlessness, ataxia, hyperexcitability, and convulsions and death within a few hours. The symptoms and period of survival vary somewhat with dosage and route of administration. At LD_{50} doses in various species death is delayed, usually until the third or fourth day, during which time notable systemic effects are consistently demonstrable. Salivation, vomiting and defecation or diarrhea, and (in mice and rats) secretion of red tears may follow immediately upon intoxication. Presumably these changes arise from a parasympathomimetic action which may or may not reflect a "cholinergic" action on the end organs. These acute effects should be distinguished from the delayed vomiting and persistent diarrhea which are probably attributable to local intestinal lesions. Intestinal hemorrhage may cause a bloody diarrhea which is rare in rodents but often seen in dogs, goats, and cats. Two additional and invariable signs of intoxication are anorexia, probably referable in part to intestinal injury, and weight loss. The weight loss is not due entirely to anorexia, a considerable part resulting from loss of electrolyte and water in the diarrhea, vomitus, and possibly urine. This condition is analogous to that seen in intestinal obstruction, cholera, and dysentery, where fatal oligemia can result in from 3–5 days. The symptoms vary with the species. Gastritis and enteritis with diarrhea may not appear in rodents, except after oral administration or after licking topically applied H; however, the stomach and small intestine are often distended and filled with a yellow viscous material.[8,23b,l,m,n,26a,c,27a,47,52,53,55r,56l,c,70,88,98,104d,105r,106a,d,121,123a,c,125,126]

After skin application of supra-LD_{50} doses in dogs, in many instances a period of increased neuromuscular excitability is followed by one of depression, and convulsions do not appear at all, although salivation and defecation are present.[104d] This neuromuscular excitability is not associated with a low blood level of total or ionic calcium.[104d]

Anesthesia may influence symptomatology and survival time in dogs after intravenous injection of supra-LD_{50} doses. Bradycardia and hypotension, which appear early in dogs under barbital anesthesia or morphine sulfate and are evanescent, are seen only preterminally in conscious dogs. Although anesthesia abolished retching and vomiting, the dogs survived only 4–6 hours, whereas conscious dogs lived 3–4 days.[56l,c]

In goats, within a few hours after skin application of a sub-LD_{50} dose of mustard, the local edema may be so severe that a reduction in plasma volume, hemoconcentration, and a shock-like state result. These developments are accompanied by leucocytosis, a slight to moderate rise in plasma nonprotein nitrogen (NPN), and a transient increase in respiratory rate and rectal temperature. After reaching a peak at 16 hours, all the above values return to normal by 21 hours. Plasma transfusions given soon after intoxication prevent the above changes.[24]

Gassing with massive doses of H vapor results in virtually the same clinical changes as intoxication by parenteral injection or cutaneous application.[55r,104d,e] However, salivation, vomiting, and weight loss did

not occur when the head of a dog was protected from H vapor, while only the body was exposed.[106d,e]

Blood Studies

A reduction in the number of white blood cells as well as various biochemical changes in the blood follow parenteral injection or cutaneous application of LD_{50} or greater doses of H. Blood platelets are markedly decreased in severely intoxicated dogs, but apparently not in other species.[58] The red blood cells are apparently little affected. The reduction in white blood cells involves both granulocytes and lymphocytes. This leucopenia affords a good index of the severity of intoxication and possibly weakens the defense of the animal against infection. It may be preceded by leucocytosis lasting a day or more.[5,26c,e,43,47,52,56d,e,f,58,63,70,93,106,122] In animals gassed with H, leucocytosis, leucopenia, and lymphopenia may or may not occur. Respiratory tract inflammation due either to the direct action of H or to superimposed bacterial infection may frequently produce a leucocytosis at a time when leucopenia would otherwise appear.[5,16b,22a,55c,86]

A hemoconcentration indicated by increased red blood cell count, per cent hemoglobin, and hematocrit may rapidly follow intoxication. This has been observed in various species after parenteral, topical, and vapor intoxication.[5,47,56d,69,70,106] As a rule, the hemoconcentration is less striking in rabbits than in other species.[47,52] In surviving animals, at a time when the leucocyte count may be returning to normal or above, a progressive anemia may occur,[69,70,106] with no alteration of the reticulo-endothelial system.[63] In rabbits and dogs this anemia frequently resembles the idiopathic or benzene type. The hematocrit, per cent hemoglobin, and red blood cell count decrease with no change in the color index, mean corpuscular volume, or diameter as measured by the Price-Jones method.[69,70,106] Thus it appears that the marrow produces fewer red cells for a time, and that in some instances the cells are immature.[69,70,106] The delayed anemia may reflect an initial injury of the erythroblastic tissue which, because of the longer life of the red cells, is not evident during the first few days of intoxication. Intestinal hemorrhage may also contribute to the anemia. Since red cells are readily digested, the stool may not be frankly bloody except in extreme instances. Hemosiderosis, typically present, indicates a marked destruction of red cells in the body.[8]

Definite changes can be demonstrated in blood obtained from intoxicated animals. An increased sedimentation rate of red cells, increase in coagulability of the blood, and an increased tendency to agglutination of cells have been observed. Red cell fragility is not altered. These changes are marked after LD_{50} or greater doses of H injected parenterally. Markedly increased agglutination may indicate that the changed properties of the red cells contribute to increased cell destruction *in vivo* as well as to the ultimate circulatory failure which appears to be the immediate cause of death.[8] An increase in sedimentation rate of red cells has also been found in rabbits from 24 hours to 4 days after cutaneous application of a sub-LD_{50} dose of H. In many instances the sedimentation rate returned to normal concomitantly with healing of the cutaneous lesions. It is believed that changes in the plasma were responsible, because normal corpuscles in plasma of treated animals sedimented faster than corpuscles of treated animals in normal plasma.[66]

Biochemical studies of blood reveal no definite and significant changes in blood creatinine, bilirubin, inorganic phosphate,[122] total acid-soluble phosphate, phosphate liberated from ATP in the blood,[12] and calcium (total or ionic)[106d,122] after parenteral intoxication with LD_{50} doses of H. On the other hand, fairly consistent changes have been noted in plasma protein, NPN, urea, chloride, glucose, pentose, cholesterol (total and free), phospholipids, fibrinogen, phosphocreatine, phosphopyruvate, and lactic acid. Less consistently and definitely, alterations occurred in blood phosphatase.[122] (CO_2)-combining power,[56f,122] and the albumin-globulin plasma protein ratio (A/G).[12,34,43,44,52,55a,56d,f,h,57c,58,63,70,93,96,106d,122]

Total plasma protein concentration decreases in rabbits and goats after skin application of H [70] but after intravenous injection may increase in dogs and cats within 2¼ hours,[56f,106d] or remain constant in rabbits.[12] An increase in the volume and specific gravity of thoracic duct lymph is associated with hemoconcentration and increased protein concentration in dogs and cats after intravenous intoxication.[56f,106d] The A/G ratio does not consistently change in rabbits,[70] dogs, and cats,[56f,106d] but decreases in goats.[70]

An alteration of the electrophoretic pattern of plasma has been reported. A decrease in the albumin fraction and an increase in the α-globulin fraction with no consistent or marked changes in the remaining globulin fractions occurred in dogs severely intoxicated with H by all routes of administration, or

with HN1, HN2, or HN3 (only intravenously intoxicated animals studied). These changes in the electrophoretic pattern appear to be nonspecific, because they were present also after burning and freezing the skin, exposure to X rays, bone fracture, and intradermal injection of turpentine. The patterns were unlike those seen in many infectious diseases.[53]

A rise in NPN (chiefly urea) after parenteral intoxication usually occurs as the animal grows weak and loses body weight but sometimes appears only terminally.[12,30f,51c,70,93] It serves, at least in rats and rabbits, as a sensitive indicator of intoxication, correlating well with outward manifestations of toxicity.[12] This rise is not seen after intraperitoneal or intramuscular injections in rabbits,[42,82] or after inhalation in rats [12] and dogs.[34]

Plasma chloride usually decreases, the extent depending on the dose and route of administration.[12,34,42,82,86f,122]

The following studies have not been informative: blood glucose levels,[12,34,42,44,82,86a,f,86h,57c,58,98] and oral and intravenous glucose tolerance.[86a,c,f,g]

A threefold rise in blood pentose occurs in dogs 30–60 minutes after intraperitoneal injection of a supra-LD_m dose of H. The rise is not definitely related to the increased hematocrit or glucose, but parallels the increase in plasma inorganic phosphate. It is not prevented by three units of insulin given intravenously 30 minutes before intoxication.[57b,c]

Total cholesterol increased in severely intoxicated dogs.[58] It increased simultaneously with an increase in blood NPN in rabbits after intravenous injection, and in rats after intraperitoneal injection.[12] A significant prolonged rise in plasma fibrinogen occurred in goats after skin contamination [122] and in rats and dogs after intravenous injections.[58] A striking correlation between the increase in fibrinogen and both free and total cholesterol has been observed in dogs after intravenous injection and cutaneous application of H. A rise in plasma phospholipids paralleled the rise in total cholesterol. These same changes occurred in HN1, HN2, and HN3 intoxication.[58] A decrease in phosphocreatine and an increase in phosphopyruvate and lactic acid occurred in rats gassed by exposure of only the body [12] and after skin application.[58] The *p*H of the blood did not change in gassed dogs.[34] Arterial oxygen saturation fell to 75 per cent 45 minutes after supra-LD_m doses of H given intravenously to dogs under barbital anesthesia, although the lungs at death were not edematous or engorged.[86d] After gassing, arterial oxygen unsaturation can result from direct respiratory injury and may conceivably lead to the death of the animal.[30]

Definitive Studies Based on Gross Clinical Observations

Parasympathetic Nervous System. Parasympathetic activity is believed to be responsible for the salivation, lacrimation, miosis, defecation, bradycardia, hypotension, and the early vomiting and diarrhea seen after H intoxication. This overactivity might result from (1) increased discharge in efferent fibers elicited reflexly or by central stimulation, or (2) from a direct action of H on peripheral effectors. Evidence for the peripheral action of H is as follows: (1) denervation of the salivary glands does not prevent the stimulating action of H on salivation,[105a] (2) atropine, except in very large doses given before intoxication, does not prevent salivation,[86d,e,105c] (3) vagotomy does not prevent bradycardia, hypotension, or the increase in motility of intestine *in situ*,[86d,e,105c] (4) miosis, typical of a general parasympathetic discharge, may be absent,[25] and (5) H reversibly depresses the contractility of both the normal and atropinized isolated frog heart.[19a]

During H poisoning there is an electrical hyperexcitability of the vagus (muscarinic effect) followed by paralysis (atropine-like effect). In the dog given intravenous H or exposed to H vapor, there is a marked depressant effect of H on the heart, decreasing the force of contraction of both auricles and ventricles, and impairing A-V conduction, sufficiently in some instances to produce partial A-V block. The arterial blood pressure slowly falls and the heart may resume its normal rate. At this stage or before, the heart does not respond to strong vagal stimulation. With convulsive doses of H, the blood pressure rises during a seizure, and falls again afterward. It decreases fairly rapidly before death. In the cat at this stage the intravenous injection of a strong dose of acetylcholine produces a marked rise in blood pressure. H, therefore, has a clear atropine-like effect in the advanced stage of poisoning. The muscarinic effect is characterized in the earlier stage when atropine fails to antagonize the effect of H and the heart remains slowed. However, if atropine is injected in large doses before H, the muscarinic effect on the heart is suppressed.[19a,102a,109]

It had been postulated that the action of H might be due to a slow accumulation of acetylcholine resulting from the inhibition of cholinesterase in the body.[19c,d] However, the fact that atropine can abolish

the cardiac slowing produced by the injection of acetylcholine but not that produced by H intoxication seems to indicate that the slowing after H is not due to the accumulation of acetylcholine.[105a]

Barbital, ethyl urethane, sodium pentobarbital (Nembutal), sodium amytal, ether, and sodium bromide were effective in eliminating vomiting in dogs after intravenous H. Sodium amytal appeared most promising, for it prevented all vomiting with only slight general depression of the animal.[56c]

H stimulates the secretory activity of the salivary glands of dogs and cats. This is due probably to an action on the gland itself, inasmuch as the phenomenon remains unaltered after section of the secretory nerves. During poisoning there is a hypersensitivity of the chorda tympani (a muscarine-like effect) followed by a progressive paralysis (an atropine-like effect).[56c,f,104g 105a,109]

H injected subcutaneously in a wide range of doses stimulates the secretion of gastric juice in conscious dogs. Since essentially the same response is elicited in animals with no vagal supply to the stomach (Heidenhain pouch dogs) as in animals with a vagal supply (Pavlov pouch dogs), the stimulation is more probably due to a direct stimulation of the secretory cells via H circulation than to reflex excitation through the vagus.[105a] H (and HN2·HCl) produce secretions from the cannulated stomach and duodenum of decapitated and decerebrated cats. These were true secretions and not transudates and, when once started, could not be prevented but merely reduced and made more viscous by large doses of atropine.[79] Direct application of H to the gastric mucosa of dogs with Heidenhain pouches depressed acid secretion but increased the volume of fluid.[105b] This flow was not copious nor continuous and so did not resemble the flow of intestinal secretion observed after direct application of H to the intestinal mucosa.[105a] This circumstance suggests the possibility that the stimulation of gastric secretion after parenteral injection may not be due to H itself, but indirectly to some sequel of H intoxication.[105b] Histamine has been suggested.[79]

The increase in the external secretion of the pancreas, starting about the same time as salivation in cats and dogs (under ether or chloralose anesthesia) after the subcutaneous administration of H, was not antagonized by atropine, given before or after intoxication.[56a] A detailed quantitative study in dogs under different conditions (after ligation of the pyloric valve or the common bile duct, or after section of the cervical vagi) suggests that this response may be due to both an indirect action through secretin, and a direct action of H on the gland cells.[104b,109]

H, unlike the parasympathomimetic drugs, pilocarpine, eserine, and acetylcholine, fails to increase the secretion of bile.[91,104h 109] However, it directly stimulates contractions of the gall bladder resulting in discharge of bile.[104h,109]

A stimulation of secretion from the small intestine was produced by parenteral injections [72,105a] or direct application [105a] of H to the intestinal mucosa of cats and dogs. This secretion was qualitatively different from that obtained from normal animals; it was pink, turbid, odorless, had a low chloride and protein content, little or no buffering power, and only a small amount of diastase activity. Thus it was difficult to ascertain whether this was a true secretion of the mucosa or simply a transudate resulting from an increased permeability of the mucosa.[105a]

The motility of isolated loops of dog small intestine with or without vagal connections is increased.[105a] Intestinal motility produced by vagal stimulation is gradually depressed. However, H does not alter the response of segments of rat jejunum to pilocarpine, adrenalin, and atropine added to the suspension baths.[56c] After direct application of H in sublethal doses, the motility of isolated loops of intestine may be initially depressed, then stimulated,[105a] or initially stimulated and then depressed,[105b] gradually returning to normal in either case.

Water and Electrolyte Metabolism. The early observations that H has a marked effect on water and electrolyte metabolism in the dog [127] have been confirmed recently.[12,56c,h] In dogs given 1 mg kg of H intravenously, a negative water balance accompanied by increased intake appeared during the first 24 hours and continued until death on the third or fourth day. Tissue water content did not change, and the decreased serum chloride and CO_2-combining power indicated that severe diarrhea rather than vomiting was the chief factor in the dehydration.[56c]

When elimination of water and electrolyte loss from the bowel was attempted by partial enterectomy in fasting dogs [a] the subcutaneous injection of 2 *L.D.*$_{50}$ doses of H resulted in (1) a retention of water without chloride during the first 24-hour period, followed by (2) the excretion of approximately the same volume of extra water during the second 24-

[a] Removal of small intestine from opening of pancreatic duct in the duodenum to the ileocecal valve.

hour period. This cyclic upset of water balance was not dependent upon an increased intake of water, and was not due to retention of extra water overnight in the stomach or colon as a result of interference with their functions by H. An increased rate of weight loss, increase in nitrogen and chloride excretion, and a negative fluid balance were present only when diarrhea and vomiting occurred (in 3 7 dogs), suggesting that the factor of prime importance in weight loss after H is the loss of fluid from the bowel, rather than an increased tissue catabolism.[106] In this study no account was taken of the possible role of the kidney which others have considered significant in intoxication by the β-chloroethyl vesicants. (See "Special Studies on HN3 Intoxication," Section 22.6.1.)

In rats given an intraperitoneal injection of H and in rabbits given H intravenously, urine uric acid and creatinine excretion were normal. The total nitrogen remained normal or showed a slight increase despite the marked fall in food intake, indicating enhanced endogenous catabolism of protein. Urine NPN (chiefly urea) decreased, the low point in urea coinciding with the peak in blood NPN (chiefly urea). The undetermined nitrogen increased at the expense of the urea fraction and was not due to ammonia excretion. There was an increase in inorganic phosphate, but chloride fluctuated. A phenol red excretion test indicated an impairment of renal function by the third day and correlated well with toxic symptoms.[12]

In rabbits given a sub-LD_{50} dose of H cutaneously, the urine urea output increased markedly, associated with an increased blood urea, but remained constant in fasting normal animals. The increased output was associated with a decreased urine volume. The creatinine output, remaining constant in fasting normal animals, rose slightly for the first 2 days after intoxication, then fell along with body weight. Microscopic examination revealed no kidney damage.[70]

The intravenous injection of urea (1 g kg) soon after the skin application of H to dogs under sodium barbital anesthesia produced diuresis resulting in anhydremia and hemoconcentration with no appreciable change in the blood pressure, or in excretion, plasma level, or clearance of urea. Later, as the circulatory system failed and the blood pressure decreased, a similar injection of urea resulted in oliguria with a rise in plasma urea and a decrease in the urea clearance. It is apparent from the above experiments that up to a certain limit renal function after H intoxication is normal. However, even though the blood pressure does not fall, in moderate degrees of hemoconcentration the kidney in H intoxication appears to be less capable of eliminating increased amounts of urea than under normal conditions. This suggests a partial failure of peripheral circulation with a normal blood pressure.[70]

A significant decrease in plasma volume has been observed in goats and rabbits after cutaneous intoxication by LD_{50} doses of H.[70,93] In dogs, after intravenous injection, total erythrocyte volume was reduced although plasma volume remained normal.[56b]

From urine and blood studies and gross clinical observations, it is evident that after parenteral intoxication with LD_{50} doses of H, exsiccation and oligemia occur after the second or third day when loss of electrolytes and water in the diarrheic stool, vomitus, and urine and or accumulation of fluid in the stomach and intestines have reached severe proportions. It is possible that loss of plasma protein in the stool contributes to the exsiccation.[8]

In H-gassed dogs, urine analysis revealed only slight alterations in volume, specific gravity, sugar, albumin, chloride, titratable acidity, total nitrogen, urea, ammonia, and creatinine. A phenol red excretion test was normal.[24] In rats exposed to H vapor (body only), a parallel increase in excretion of inorganic phosphate and total nitrogen occurred, suggesting in this instance an intracellular origin of nitrogen.[56b]

Prophylaxis and Therapy of Systemic Intoxication

Prophylactic and therapeutic procedures aimed at the reduction of mortality and the prevention or alleviation of systemic symptoms due to H have on the whole been unsuccessful. Mortality was not affected by the following procedures initiated before intoxication: atropine, eserine, and ascorbic acid injected subcutaneously prior to the subcutaneous injection of H;[106] and certain compounds with high competition factors (see Chapter 19) as well as other compounds, many containing sulfur, injected intraperitoneally immediately prior to cutaneous application of LD_{50} or greater doses of H.[10,22a,92,106a] However mortality was reduced by the intraperitoneal injection of crude biotin[56a] and certain compounds with high competition factors immediately before cutaneous application of H. Administration of crude biotin 2 hours before contamination produced a slight reduction in mortality which was not apparent when pure crystalline biotin was used in place of the crude

preparation. This circumstance could have resulted from a beneficial effect of an impurity in the crude material.[86a] A 40 per cent reduction of mortality attended the prophylactic use of sodium monoethane dithiophosphonate, potassium diethyl dithiophosphate, potassium diethane dithiophosphonate, hexamethylenetetramine (HMT), sodium thiosulfate, and potassium thioacetate.[10,92]

Many procedures initiated after intoxication have not affected mortality. Fluids, balanced salt and sugar intravenously and subcutaneously, or the intravenous infusion of amino acids[b] did not reduce the mortality or otherwise affect systemic symptoms in dogs due to the intravenous injection of LD_{50} or greater doses of H. Atropine in large single or repeated doses injected into rats, rabbits, guinea pigs, cats, and goats after contamination with or injection of H (or HN2) failed significantly to influence mortality, although survival time increased.[92] BAL given intraperitoneally to rats 6 hours after the intravenous injection of H actually enhanced the toxicity instead of exerting any protective action.[23a] Other chemical compounds including some with high competition factors had only a very slight effect on mortality when injected intravenously or intraperitoneally 0 5 minutes after cutaneous application of 1 2 LD_{50} doses of H.[87,92]

Leucopenia, likewise, has not yielded to prophylactic or therapeutic procedures. Pentnucleotide is ineffective.[111] Rabbits were not protected from the leucotoxic effect of an intravenous injection of H by the following substances given intravenously 3 days before intoxication: liver extract, morpholine derivative of H, thiodiglycol, amino derivatives of H, thiourea addition product of H, half xanthate of H, potassium dixanthate derivatives of H, sulfonium salt of H, sodium diethyldithiocarbamate, sodium bisulfate, sodium sulfide (alone or after sodium nitrite), sodium bisulfite, thiourea, zinc thiocyanate, lipoid-rich serum globulin fraction, urotropine, and sulfanilamide.[23d,e]

In dogs intoxicated intravenously by LD_{50} or greater doses of H, the hypotension which developed was only temporarily improved by the intravenous injection of pituitrin and large amounts of adrenalin.[23d,e]

Neither weight loss nor diarrhea were affected by the subcutaneous administration of adrenal cortical extract, desoxycorticosterone acetate, or ascorbic acid in rats contaminated with LD_{50} doses of H.[92]

In certain species (guinea pigs, rats, and goats), atropine in large single and repeated doses reduced the weight loss after H and HN2, especially H, but did not alter hemoconcentration, leucopenia, or mortality. Diarrhea in cats and goats was not prevented by continued atropinization.[92] Other attempts to eliminate systemic symptoms believed to be due to overactivity of the parasympathetic nervous system have already been described above under "Definitive Studies Based on Gross Clinical Observations."

Miscellaneous Studies

Occlusion Experiments. Occlusion of the blood supply to various organs may prevent injury by H to the tissues involved. In the rabbit, occlusion of the abdominal aorta and a mesenteric artery during and for 15 minutes following the intravenous injection of 4 mg kg of H dissolved in propylene glycol protected the femoral marrow and that portion of the ileum supplied by the clamped vessel against the action of H.[23a] The results in the rabbit show that the action of H is rapidly completed after injection. No support is apparent in these experiments for the prolonged circulation of derivatives of H which might act over long periods and thus account for the delayed appearance of some lesions.

In the rat, partial protection was afforded the femoral marrow against a dose of 1 mg kg by occlusion of the abdominal aorta during and for 15 minutes following the intravenous injection of a solution of H in propylene glycol. This procedure was ineffective against a dose of 2 mg kg of the same solution. Occlusion for periods up to 60 minutes did not protect the femoral marrow against a solution of H in thiodiglycol at doses of 1 and 2 mg kg.[23a,c,102] The failure of occlusion to protect against the solution of H in thiodiglycol is unexplained.

The successful protection by occlusion depends on the time during which H circulates in a free form in the blood. In the intact animal, presuming a homogeneous solution of H in the blood, the disappearance of H is measured by (1) its reaction with water and other constituents of the blood, and (2) its diffusion out of the blood. Reaction 1 has been measured *in vitro* and found to vary with the species.[23a,b,28,29] In rabbit blood, *in vitro*, the half life of H at 37 C is 11 minutes.[28] The half-life *in vivo* is certainly less than

[b] A mixture of synthetic amino acids[86a,b,c] and Amigen (an enzymatic casein hydrolysate) or an acid hydrolysis of animal tissue were used. Amigen may actually increase mortality and the incidence of leucopenia.[6]

11 minutes, since H is disappearing as a consequence of reaction 2 as well as of reaction 1.

Effect of Lipemia on Survival Time. Lipemia following ingestion of olive oil 3 hours before intoxication by LD_{50} doses of H subcutaneously or intravenously may hasten death in rabbits.[56c]

Colloidal Gold Curve of Cerebrospinal Fluid. Typical human tabetic colloidal gold curves of cerebrospinal fluid (cysternal puncture at 3 hours, 72 hours, and 7 days) were obtained in goats gassed at LCt_{50} doses (Ct = 2,520 mg min m^3, t = 3 hours) of H indicating possible involvement of the central nervous system. Rabbit curves were altered, but less typically.[31]

Tissue Analyses and Weight of Organs. In male rats given sub-LD_{50} doses of H cutaneously, the ascorbic acid content of the adrenal glands decreased and liver glutathione increased, no change occurring in liver and spleen ascorbic acid, or adrenal and spleen glutathione.[49] In the rat after intravenous injection, adrenal ascorbic acid did not change, but total cholesterol decreased with a marked increase in the per cent of free cholesterol.[58] (See Section 22.5.1 for detailed analyses of adrenals after H intoxication.) In the rat after intravenous injection of H (also HN1, HN2, or HN3) there was no change in liver lipids and prothrombin time, but liver glycogen increased. In dogs clotting times were not constant.[58] There is no decrease in the acid-soluble phosphate of skeletal muscle on the first day after gassing, and a small but significant decrease on the third day[55a,56i] in rats gassed at a Ct of 7,500 mg min m^3, fasted from 20–22 hours beforehand, and given no food but water *ad libitum*. Further analysis of muscle on the first or third day after gassing (animals given pentobarbital anesthesia prior to killing) showed no change in total glycogen or inorganic phosphate. Phosphocreatine and readily hydrolyzable phosphate were unchanged on the first day, then decreased on the third day. Lactic acid changes were indefinite.[55a] Total body protein, NPN, carbohydrate, neutral fat, ash, and water were not selectively depleted in rats dying 84 hours after intoxication by subcutaneous H, although body weight was reduced.[55a] The weight of the gastrointestinal tract of fasted rats on the third day after body-only exposure to H vapor was greater than that of fasting normal animals.[56i] Both groups showed the same decrease in total body weight, weight of liver, heart, spleen, kidneys, and muscle on the first and third days. Brain weight did not change.[56i]

Sensitization to H. No sensitization to H, as judged by mortality, body weight loss, and pathology, resulted from the repeated intravenous injections in dogs of from 0.05–0.5 mg/kg of H, 2–5 times at 30-day intervals.[56a] Rats did not develop a greater tolerance or an increased sensitivity to H after several weeks of daily ingestion.[129]

Effect of H on Magnesium-Sensitized Animals. Subanesthetic doses of magnesium (60 mg/kg), or of manganese and calcium, potentiate the toxic action of an LD_{50} dose of H subcutaneously in mice, similar to the action of magnesium on adenine nucleotide toxicity and traumatic injury. One ml of plasma removed from H-intoxicated dogs at frequent intervals after intoxication and injected into mice sensitized with magnesium produced only occasional deaths. Either the dose was too small or breakdown of the toxic compound was too rapid.[27b] The serum of rats and rabbits intoxicated with H contains no factor which inhibits the oxygen consumption of *Trypanosoma equiperdum*, indicating the absence of histone bodies (the toxic proteins liberated by the breakdown of nucleoproteins) and protamines.[12,17d]

Elimination of Bile from Intestine. Elimination of bile from the intestine by producing a biliary fistula did not prevent the development of gastrointestinal congestion and hemorrhage, diarrhea, or leucopenia after subcutaneous injection of LD_{50} doses in dogs, rabbits, and goats.[91]

Effect of Diet. Varying the fat content of the diet did not alter the mortality or clinical symptoms in rats receiving lethal or sublethal doses of H mixed with their food.[125]

Effect of Climate on Toxicity. The symptomatology and survival time of mice after subcutaneous administration of H were not affected by alteration of temperature and humidity during the period of intoxication.[121]

Capillary Permeability. H was found to be a lymphagogue of the first class, causing an increase in lymph flow from the thoracic duct in dogs.[102] However, the rate of disappearance of Evans blue dye from the blood was decreased, suggesting a decrease in the loss of albumin.[56f] An increase in permeability of the capillaries of the small intestine of the rat to trypan blue has been suggested since the intestines were more deeply stained with this dye than were other organs or those of normal animals.[123a] A capillary permeability factor, believed not to be histamine, but identical with or similar to the leukotaxine isolated by Menkin from nonvesicant inflammatory exudates, has been isolated from vesicant blister fluids produced by H (and HN2) and from the prod-

TABLE 2. Systemic effects in rats of LD_{50} doses of H.

These data are an average of data reported in detail.[1] The abbreviations iv, sc, cut, and gas represent intravenous, subcutaneous, cutaneous application, and exposure of the whole body to the vapor, respectively. In the cases of intravenous and subcutaneous administration, the H was dissolved in propylene glycol.

Route \ Lesion	Total systemic injury	Lymphoid atrophy	Myeloid injury	Leucopenia	Enteritis	Weight loss
Iv	Moderate	Severe	Moderate	Severe	Moderate	Moderate
Sc	Moderate	Moderate	Severe	Moderate	Severe	Moderate
Cut	Mild	Mild	Mild	Mild	Mild	Moderate
Gas	Mild	Mild	Mild	Moderate	Absent	Mild

uets obtained by incubating plasma and serum with H.[33] Of interest in this connection is the observation that leukotaxine, which is rapidly destroyed by normal serum, is not destroyed by serum from rabbits after either skin contamination with H or thermal burning.[30] A capillary permeability factor has been demonstrated in rabbit corneas 20–24 hours after exposure to liquid H.[28] H increases the permeability to dyes of the salivary glands and pancreas but not of the choroid plexus and meninges, resulting in the elimination of indigo carmine via the saliva and pancreatic juice.[1a,c,h]

Cross-Transfusion Experiments. Cross-transfusion experiments have provided no evidence for a circulating toxic principle early after intoxication. A normal dog was cross-circulated with an intoxicated dog 30 minutes after receiving a supra-LD_{50} dose of H intraperitoneally when all traces of H had disappeared from the blood. In every instance, the cross-circulated normal animal survived while the injected animal died.[37d]

22.2.2 Systemic Pathology of H Intoxication

The pathologic changes which result from the systemic action of H consist of the following:*

1. Injury to the intestinal tract, primarily the small intestine, consisting of destruction of the mucosa with desquamation and necrosis of the epithelium, and hemorrhage in extreme cases.

2. Injury to the bone marrow, with depletion of the granulocytic series and degenerative changes in the megakaryocytes, culminating in aplasia.

3. Lymphatic tissue injury consisting of fragmentation of lymphoid cells in the spleen with phagocytosis of chromatin particles and cellular depletion of the sinuses, and cytolysis of the lymphoid cells of the thymus and interstitial tissue.

These lesions were recognized by the investigators of World War I, but their origin and interpretation by the early workers differs somewhat from present ideas. There is no reason to suppose that injury to the leucoblastic organs is lethal in itself, although leucopenia may be considered an unfavorable prognostic sign (particularly in man) and it possibly weakens the organism's defense against infection. The cause of weight loss, which usually represents the most severe lesion, is not completely explained, and it has been shown repeatedly that anorexia contributes to, but does not entirely account for, weight loss. The available evidence points to the intestinal lesion as highly significant in causing death. Vomiting and diarrhea, by the consequent loss of electrolytes, water and protein, can lead to progressive exsiccation and oligemia. The latter in turn can precipitate circulatory failure, and death results from medullary asphyxia or possible cardiac failure. The earlier view that enteritis was secondary to neurogenic injury or possible local irritation has been abandoned in favor of a local cytotoxic action. The latter presumably accounts for myeloid injury and undoubtedly will be shown to be the ultimate cause of weight loss. However, the presence of other lesions of lethal magnitude in LD_{50} doses of intoxication are not certainly excluded.

The literature on the systemic action of H up to August 1, 1943 [a] and on the cytotoxic action of H [d] has been reviewed. Additional reports concerned with the systemic pathology are available.[37,56,126]

For producing visible systemic injury in rats, H is superior at LD_{50} doses to the other β-chloroethyl vesicants (HN1, HN2, and HN3) when administered intravenously or subcutaneously. However, the systemic injury which follows cutaneous application and gassing is relatively mild. Table 2 shows the

* In addition to these lesions, there may be added leucopenia and weight loss, both of which have been considered earlier in this chapter.

intensity of total systemic injury and of individual lesions in the rat following LD_{50} doses.

In the rat at sub-LD_{50} doses, no lesions were observed following skin application except a mild weight loss, and after intravenous administration lesions were infrequent and generally mild. However, following subcutaneous injection, the lesions were only moderately reduced compared to those following LD_{50} doses. Lymphoid atrophy was mild, myeloid injury moderate, leucopenia severe, and enteritis and weight loss moderate.

In intravenously intoxicated animals, lung damage has been reported by investigators of both World Wars. Following intravenous injection of a solution of H in either propylene glycol or thiodiglycol, the lung injury involves diffuse pulmonary congestion and edema, but when neat H is given rapidly, graver necrotizing and hemorrhagic lesions ensue.[29a] Pulmonary injury is not typical of all parenteral routes of administration, and it seems apparent from the experiments quoted above that lung injury occurs as a result of the localization of particulate H in the pulmonary capillary bed.

Hemorrhagic lesions in the stomach have been reported by some investigators, but generally under conditions where oral contamination may have occurred.[8,23k]

Among the dogs which died in a shock-like condition following the skin application of a solution of H in motor oil, significant systemic lesions failed to develop. The only pathologic observations were moderate splenic necrosis in 2 11 animals and hemoglobin casts in the renal tubules in 3 11. Red cells were found in the tubules in one and in the capsular spaces of the glomeruli in another. Fatty changes were present in the tubular epithelium, being severe in the distal portion of the convoluted tubules.[47]

22.2.3 Some Observations on Human Intoxication

A review of the evidence from soldiers gassed or burned by H in World War I indicates that essentially the same systemic effects as seen in experimental animals were present in varying degrees.[8,11] Vomiting, appearing shortly after exposure, is invariably present after intoxication by mild doses. However, more delayed gastrointestinal disturbances, namely anorexia, epigastric pain, persistent gastric intolerance, constipation, or, in more severe cases, diarrhea, which recur in many clinical descriptions, depend on the severity of injury from gassing or skin contamination. Anorexia and gastric intolerance may extend over a period of months, leading to extreme cachexia and asthenia and prolonged convalescence, with return of appetite considered one of the best prognostic signs. A feeling of constriction of the chest, loss of weight, and increased body temperature also have been reported. Various neurological disturbances may occur and consist of the following: frontal headache, drowsiness and lethargy, apathy, somnolence interrupted by states of excitement, tremor, and, in some cases, sudden deep coma with or without terminal motor paralysis. However, central nervous system injury appears only in the most severe cases of intoxication. Comments on circulatory changes seem uncertain. Bradycardia is present early in intoxication. Tachycardia and hypotension appear later, indicating circulatory insufficiency.[20,22,84,98,114,118,127–132,135]

In masked volunteers exposed to H vapor, vomiting is a much more marked symptom in the tropics than in temperate zones.[64,127] "In temperate climates, severe vomiting is usually only observed with the comparatively rare fulminating cases; in the tropics, it is a usual feature of even moderately severe cases."[127] In gassed volunteers masked and wearing protective clothing, vomiting may occur with comparatively small doses (Ct = 400 mg min/m³) and can be violent, frequent, and prolonged with somewhat larger doses (Ct = 600 mg min/m³).[127] Nausea and vomiting may be present without evidence of oral intoxication[112–115] or persistent intestinal disturbances.[11] Nausea, vomiting, anorexia, and persistent intestinal disturbances may be absent in volunteers sublethally gassed under tropical conditions[134] and in men accidentally suffering H third-degree burns,[11] and may occur without any evidence of enteritis. A leucotoxic action need not be associated.[112,113,115] Since nausea, vomiting, and depression can be elicited by an inflammatory reaction produced by radiation, trauma, or fire burn, these symptoms do not offer *prima facie* evidence of systemic intoxication by mustard, at least in man. They are more likely a nonspecific response to skin damage.[11,61]

Men accidentally suffering prolonged skin contamination by a mixture of liquid H in oil showed evidence of systemic intoxication, namely, increased body temperature, hypotension, increased pulse, and apathy, but no other symptoms of peripheral circulatory failure, such as restlessness, anxiety, acute distress, or cold extremities.[57,60] A similar clinical picture appeared in men accidentally contaminated

with liquid H.[97 99 112 115,120] Detailed clinical histories of H fatalities are available.[59 60,98 99,112,113,115,139] In the case of men contaminated by a mixture of liquid H in oil, some deaths occurred as early as 18 hours after contamination before there were marked visual evidences of skin damage. Individuals appearing in good condition except for hypotension (40 60 mm Hg), conjunctivitis, and skin erythema, within a matter of minutes became comatose and rapidly died without showing any prognostic signs. Failure of the peripheral vascular bed seemed profound in severe cases; in any event, the patients were incapable of responding to shock therapy, i.e., the administration of warm fluids plasma transfusions, and morphine. Injections of adrenalin, other vasotonics, and coramine gave only vague transient effects. Circulatory failure was considered primarily peripheral, inasmuch as the hypotension was severe without marked tachycardia and respiratory changes, and inasmuch as the diastolic pressure in surviving cases was highly labile, never rising to a level comparable to the rise in the systolic pressure.[59,60]

Marked leucopenia and loss of reactivity of the bone marrow, which are observed in experimental animals after parenteral intoxication with LD_{50} doses of H, are seen in man only in the most severe cases of intoxication. In masked volunteers, sublethally exposed under temperate or tropical climatic conditions to liquid H or to H vapor (*Ct* of from 50 760 mg min m^3), there is a moderate to marked leucocytosis appearing as early as 4 hours [118] or later [34] and consisting essentially of increases in neutrophilic polymorphonuclear leucocytes and lymphocytes. In some instances this was followed by a mild to moderate leucopenia,[126] but more frequently by a continued gradual increase in neutrophilic polymorphonuclear leucocytes and lymphocytes, with no demonstrable change in eosinophilic or basophilic polymorphonuclear leucocytes or large mononuclear leucocytes.[34,129 120,133] There appeared to be no correlation between the severity of the resultant burns and changes in the white cell count, nor with toxic symptoms such as vomiting, headache, nausea or anorexia,[129,130] and leucocyte changes may be absent, although nausea and vomiting occur.[33] Blood changes after exposure under tropical conditions have been observed in gassed volunteers at *Ct*s very much lower than would be considered necessary to produce them under temperate conditions.[131] Unprotected men splashed by H had a marked leucocytosis on the first day, dropping to normal by the eighth day, but no leucopenia.[97] Irritation cells (Türck) have been found, indicating an upset of lymphopoietic tissue.[101]

In fatally intoxicated men, a marked leucopenia of 300 was noted 12 hours before death in one instance [112] and on the tenth day (9 days before death) in another.[115] In the latter instance, leucopenia was possibly influenced by the use of sulfathiazole. A marked leucocytosis was noted in many of the cases at Bari.[59 60] Fatally contaminated men usually developed a severe leucopenia reaching levels as low as 50 cells mm^3 by the third or fourth day in many instances.

Little change in the red cell count has been noted in volunteers exposed to various amounts of liquid H or H vapor. The relatively long life period of the red blood cells tends to maintain the cell count through the acute illness, while exsiccation, where present, may produce hemoconcentration in the face of possible erythroblastic injury. As in experimental animals, anemia may follow after a considerable delay.[8] Hemoconcentration, seen on the day of admission in men contaminated by H in oil, was corrected by the second or third day in those individuals surviving this period, and, therefore, can be considered an unimportant factor in subsequent delayed deaths.[59,60] A decrease in red cell count has been reported in other fatalities.[99,112] Thrombocytopenia has not been observed in men severely burned by H, although it has been reported after intravenous intoxication by HN3.[81]

A decrease in coagulation time in gassed soldiers was noted in World War I [141] and has been confirmed in this war [120,132] in volunteers exposed to liquid H under tropical conditions. These observations suggest an interference with liver function. Exposure to liquid H by contact in field observers resulted in an accelerated sedimentation rate in each of three cases.[34]

Analyses of urine from men intoxicated by H are few and very incomplete. A trace of albumin was occasionally found in the urine of Bari casualties but there was no hematuria.[60] In a man suffering contamination of 85 per cent of his body surface with liquid mustard, the urine 137 hours after exposure (37 hours before death) was acid, bilirubin positive, and contained considerable albumin but no red cells.[112]

The literature on the pathology in humans fatally exposed to H has been reviewed up to August 1, 1943.[8] Since that time additional information has accrued. Exclusive of damage to the respiratory

tract, a summary of the microscopic pathology of a fatality resulting from vapor exposure is as follows: acute ulceration of the first part of the duodenum; cloudy swelling, congestion (possibly post mortem changes) and cast formation in the kidney; cloudy swelling and early necrosis in the liver (possibly post mortem changes); distension of the spleen with red corpuscles; depletion of lymphoid tissue in the spleen, mesenteric, inguinal, and preaortic lymph glands with lymphoblastic proliferation; and disappearance of granulocytes and myelocytes from the bone marrow.[115] In spite of the severe systemic damage sustained by this casualty, death did not occur until early on the thirteenth day. Death was precipitated by lung edema which followed and was possibly related to the slow-drip, intravenous blood and fluid therapy inaugurated late on the tenth day. There was no late vomiting, and a late constipation occurred as the result of the duodenal ulcer and possibly a paralytic ileus. Diarrhea appeared, however, on relief of constipation by means of a turpentine enema, but was under control the day of death.

After exposure to liquid H, another casualty died at 171 hours during an attack of pulmonary edema with marked cyanosis which followed within 2 hours after a transfusion of whole blood. A marked leucopenia (300 cells mm^3) was present 12 hours before death, but macroscopic examination showed normal red marrow in the femora, humeri, vertebral bodies, and sternum, and only the tibia was without red marrow. No microscopic pathology was reported.[112]

It is debatable[49,110] to what extent systemic injury contributed to death in men exposed to H in the oil-water mixture at Bari. Blast injury, respiration of foreign material, secondary infection, and prolonged immersion were superimposed on the effects of exposure to H. Unfortunately, no sections of intestine and bone marrow from the victims were prepared for histological examination. Therefore it is difficult to assess systemic injury. However, severe systemic injury is indicated in at least some instances by a profound leucopenia. Some significance was attached to renal injury.[49] This injury consisted of tubular casts of hemoglobin and calcium, with degeneration and necrosis of adjacent tubular epithelium. However, these lesions were not sufficiently extensive to have caused renal insufficiency. The specificity of the kidney damage has been questioned,[110] and renal lesions have never been seen in experimental animals.

22.3 DERIVATIVES OF AND COMPOUNDS RELATED TO H

In Table 3 the toxicities of some of the derivatives of H and compounds related to H are tabulated. A compound with an LD_{50} by subcutaneous injection <25 mg kg arbitrarily is considered toxic; >25 mg kg, nontoxic.

β Chloroethyl β-hydroxyethyl Sulfide (ClH)

Large doses of ClH in propylene glycol given intravenously in mice produce rapid death during the transient but nonlethal convulsions produced by the volume of propylene glycol used. ClH produced enteritis, congestion, and increased hematopoiesis of the liver and injury to the lymphoid organs, with enlargement and congestion of the adrenal glands.[23a] ClH produced sensory and motor paralysis of the limb used for the intramuscular injection in rats and was toxic by this route (LD_{50} = 0.5–1.7 mg/kg).[106b]

Thioglycol (TG)

Thioglycol, unlike H, has no effect on the cardiovascular system: i.e., it does not increase blood pressure or heart rate, and does not alter vagus nerve irritability when given intravenously to dogs or rabbits.[106,1]

β-Chloroethyl β-[*bis*(β-Hydroxyethyl)Sulfonium] Ethyl Sulfide Chloride (H TG)

Analysis of extractables in pig skin tissue formed by the action of radioactive H (H*) *in vivo* shows that H TG* sulfonium salt comprises about 2.5 per cent of the radioactive material present. When 0.0008 *M* H* was reacted with blood plasma for 30 minutes at 37 C, 2.4 per cent of the added H* went to H TG*. Of the extractables formed, 3.1 per cent was H TG*, and 1.5 per cent of the H which reacted went to H TG*.[21]

H TG has no neurotoxic action even in large doses administered subcutaneously.[8] The absence of a leucotoxic effect of H TG chloride in LD_{50} doses in rodents constitutes a notable difference in the action of this compound and that of H. In mice and rabbits, moderate to severe enteritis, mild necrosis of the liver, injury to lymphoid tissues, especially the spleen, and mild to moderate adrenal congestion are seen without any bone marrow injury.[23a] In rats large doses of H TG as the picrylsulfonate produce marked diarrhea, loss of body weight, and essentially the same pathologic changes as the chloride.[23a] In dogs a slight leucopenia follows the intravenous ad-

TABLE 3. Toxicity of derivatives of and compounds related to H.

N.T. = Nontoxic by screening study; Scr = Screening
T. = Toxic by either screening or definitive study; Def = Definitive

A compound with an LD_{50} by subcutaneous injection <25 mg/kg arbitrarily is considered toxic; >25 mg/kg, nontoxic.

Compound examined	Remarks	References
A. *Compounds arising from the hydrolysis of H*		
1. β-Chloroethyl β-hydroxyethyl sulfide (ClH)	N.T.*	23t
2. Thioglycol (TG)	N.T.*	23q
3. β-Chloroethyl β-[*bis*(β-hydroxyethyl)sulfonium] ethyl sulfide chloride (H HTG)	T. (def)*	23q,u,x, aa, 76
4. *bis*[*bis*(β-Hydroxyethyl)sulfoniumethyl] sulfide dichloride (H 2TG)	N.T.*	16i, 23f
5. β-Hydroxyethyl β-[*bis*(β-hydroxyethyl)sulfonium] ethyl sulfide chloride (ClH HTG)	N.T.*	23i
B. *Synthetic sulfonium compounds*		
1. Methyl-*bis*(β-hydroxyethyl)-sulfonium chloride	N.T.	20e
2. *tris*(β-Hydroxyethyl)sulfonium chloride	N.T.	20e
3. *tris*(β-Chloroethyl)sulfonium chloride	N.T.	16o,p, 20e
4. β-Chloroethyldimethylsulfonium chloride	N.T.	16f
C. *Compounds arising from the oxidation of H*		
1. *bis*(β-Chloroethyl) sulfoxide (H sulfoxide)	N.T.	16d
2. Divinyl sulfoxide (TL 907)	N.T.	16i
3. β-Chloroethyl-α,β-dichloroethyl sulfoxide†	N.T.	16n
4. *bis*(β-Chloroethyl) sulfone (H sulfone)	N.T.*	23p, 107
5. Divinyl sulfone	T. (def)	23p, 107
6. *bis*(β-Hydroxyethyl) sulfone	N.T.	57a
D. *Replacement or addition derivatives of above compounds*		
1. Ethyl β-chloroethyl sulfide	T. (scr)	17b
2. Divinyl sulfide	N.T.	63
3. *bis*(β-Pyridiniumethyl) sulfide	N.T. Neurotoxic	20j, 23e
4. Diamide of *bis*(β-[3-carboxy-pyridiniumethyl] sulfide dichloride	N.T.	20k
5. $ClCH_2CH_2-\overset{S}{\overset{\uparrow}{S}}CH_2CH_2-P(OC_2H_5)_2$	T. (scr)	17c
6. $S\left[S(CH_2CH_2S-P(OC_2H_5)_2)_2\right]_2$	T. (scr)	17c
7. $O_2S(CH_2CH_2SO_3Na)_2$	N.T.	20j
8. Phenyl-*bis*(β-chloroethylthioethyl)amine†	N.T.	16j
9. Methyl-*bis*(β-chloroethylthioethyl)amine†	T. (scr)	16j
10. *bis*(β-Pyridiniumethyl) sulfone	N.T. Nonneurotoxic	20j, 23e 23e
11. Reaction product of divinyl sulfone and *l*-proline	N.T.	20l
12. *bis*(β-Hydroxyethylthioethyl) sulfone	N.T.	20l
13. *bis*(β-Hydroxyethyl)thiazanium dioxide pierylsulfonate	N.T.	20l
14. Vinyl[β-(*bis*(β-chloroethyl)-amino)ethyl] sulfone†	T. (def) Neurotoxic Nonneurotoxic	20m, 23w 23w
15. Reaction product of divinyl sulfone and strychnine	T. (def) Neurotoxic	20m, 23w
16. Reaction product of divinyl sulfone and brucine	N.T.	20l
E. *Q, compounds related to Q, and derivatives of Q*		
1. 1,2-*bis*(β-Chloroethylthio)-ethane (Q)	T. (def)*,‡	23n, 23o
2. *bis*[β-(β-Chloroethylthio)-ethyl] ether	N.T.	16l
3. 1,2-*bis*[*bis*(β-Hydroxyethyl)-sulfoniumethylthio]ethane dichloride (Q-2TG)	N.T.	23p
4. β-Chloroethyl-1,4-dithianesulfonium chloride	N.T.	16o,p, 20b, 23p
5. β-Hydroxyethyl-1,4-dithianesulfonium chloride	N.T.	20e, 102b
6. Vinyl-1,4-dithianesulfonium chloride	N.T.	20i
7. β-Pyridiniumethyl-1,4-dithianesulfonium dichloride	N.T.	20k
8. $S\begin{matrix}CH_2CH_2\\ \\ CH_2CH_2\end{matrix}S^+CH_2CH_2SO_3^-$	N.T.	20l

* Pathology and pharmacology described in text.

† Classification arbitrary.

‡ In theological: The University of Chicago Toxicity Laboratory reports LD_{50}<10 after subcutaneous injection in mice of suspension of Q in either gum tragacanth, acacia or mineral oil. The "minimum lethal dose" of an oil solution given subcutaneously in guinea pigs is from 10 to 50 mg/kg.

ministration of H-ITG as the chloride or pierylsulfonate.[23r,s]

bis[*bis*(β-Hydroxyethyl)sulfoniumethyl] Sulfide Dichloride (H-2TG, TL 510)

LD_{50} doses of H 2TG produced delayed death in mice, after intravenous or subcutaneous administration, and in rabbits, after intravenous administration. In the rabbit the compound has a leucopenic action,[23t] possibly resulting from its dissociation to H in the body. Although nontoxic (LD_{50} administered subcutaneously, approximately 200 mg/kg), this compound caused rapid death with convulsions when given to mice in large doses (350–500 mg/kg).[23u,v]

Given to rabbits intravenously in lethal doses, H 2TG produced prostration, ataxia, copious rhinorrhea and salivation, and slow, deep respiration. Massive hemorrhage and edema appeared in the lungs in animals which died within 24 hours. There was a marked leucopenia with little change in erythrocyte count.[23w]

bis(β-Chloroethyl) Sulfone (H Sulfone)

When given to rats and mice intravenously or subcutaneously, H sulfone has a marked parasympathomimetic action.[23x] After subcutaneous or intraperitoneal injection in large doses in mice, excessive lacrimation and salivation occur with marked tremors prior to death, rigor mortis rapidly following. The tremors were not alleviated by the intraperitoneal administration of atropine. Glutathione injected intraperitoneally prevented death from a lethal dose of this compound.[82] H sulfone has a pharmacological action very like H on the cardiovascular system [104] and on the salivary glands.[105a] H sulfone at a dose of 60 mg/kg intravenously in dogs caused a decrease in blood pressure and a slight modification of vagus nerve irritability, but did not alter the heart rate.[104] Supra-LD_{50} doses produced severe pulmonary injury. With lower doses there were no pathologic changes.[23y] A marked leucocytosis occurred in rabbits the second day after the subcutaneous administration of 20 mg/kg, counts returning to normal by the sixth day.[45] In mice, cats, and rabbits gassed with H sulfone, there was present slight diffuse pneumonitis, lymphorrhexis in the thymus glands, lymph nodes, and spleen, and slight parenchymatous degeneration of the convoluted tubules in the kidney. Depletion of the red pulp of the spleen and the hematopoietic tissue of the bone marrow was not complete at the time of death.[7] Following the intravenous administration of 5 mg/kg of radioactive H sulfone, the distribution of S^{35} in various tissues at 1 hour was qualitatively similar to the distribution of S^{35} after intravenous administration of H or H sulfoxide. However, after H sulfone was given, the S^{35} content in the liver was much lower than that prevailing after the other two compounds. The amount of fixed S^{35} in most of the tissues was considerably higher than after H or H sulfoxide. A considerable amount of S^{35} appeared in the urine.[105a]

Divinyl Sulfone

Divinyl sulfone has a marked parasympathomimetic action.[23z] Intravenous injection in dogs and cats rapidly produced a transient period of hypertension, followed by a progressive hypotension, cessation of salivary secretion, and a progressive decrease in the irritability of the chorda tympani. This action is quite different from that of H and its oxidation products.[106]

Supra-LD_{50} doses produced severe pulmonary injury. With lower doses pathologic changes were not apparent.[23a] A moderate transitory leucocytosis but no leucopenia appeared in rabbits after intramuscular intoxication.[45]

bis(β-Chloroethyl) Sulfoxide (H Sulfoxide)

H sulfoxide injected subcutaneously or intraperitoneally in mice caused ascites, edema, lacrimation, and salivation,[82] but appeared to be less toxic than H sulfone or H.

Studies utilizing H sulfoxide containing S^{35} showed that the sulfoxide is distributed in the same fashion as H except for the particularly high S^{35} content in the gall bladder bile compared with that in blood and other tissues.[105a]

Divinyl Sulfide

Divinyl sulfide given subcutaneously to dogs (no record of dose) produced local and systemic disturbances. The urine contained very large amounts of blood casts and bile pigments, and a copious precipitation of albumin was always obtained. Since such urinary changes did not occur in dogs given injections of pure H, there is no need for postulating that divinyl sulfide is formed when H is injected.[21]

22.3.9 1,2-*bis*(β-Chloroethylthio)ethane (Sesquimustard, Q)

Q is more toxic than H for small animals and its action is likewise delayed.[21] The principal pathologic changes in rats given LD_{50} doses intravenously or

subcutaneously are marked enteritis with only slight injury to the lymphatic tissues. There is no leucopenia nor bone marrow injury. However, in rabbits injected intravenously there is moderate to marked leucopenia. Q administered subcutaneously and intravenously exhibits the enterotoxic action to a greater degree than H, injury being evident at sub-LD_{50} doses, whereas the leucotoxic and myelotoxic actions are less marked than with H, HN1, HN2, or HN3.[23b,e] In mice gassed with Q the liver and kidney showed parenchymatous degeneration and marked fatty changes. The lymphatic tissue, including that of the spleen, was very atrophic, presumably from toxic rhexis of the lymphocytes, although this early stage was not seen. A complete aplasia of the bone marrow occurred with the replacement of the hematopoietic tissue by hemorrhage.[7]

22.4 ETHYL *bis*(β CHLOROETHYL)AMINE (HN1, TL 329, 1149, ETHYL-S)

22.4.1 Pharmacology

Toxicity

The parenteral toxicity of HN1 is shown in Table 4. In addition to these data, a dog receiving 40 mg kg of HN1 on the clipped shaved back died on the fourth day, whereas three dogs survived 10, 20, and 30 mg kg doses respectively.[36] Tolerance to a second oral dose of 2.5 mg kg of HN1, which killed 75 per cent of the control animals, has been reported in rats which received a primary oral dose of 0.75 mg kg 4 weeks previously.[27e]

Pharmacodynamics

Large doses of HN1·HCl administered intravenously or subcutaneously to mice induce disturbances of the nervous system which range from poor coordination, tremors, and weakness, to convulsions depending on the dose and route.[23k] Intravenously administered in the rabbit, 10 mg kg (approximately 3 LD_{50}) caused first a central nervous system stimulation followed secondly by depression and rapid death. Parasympathetic effects were only mild. Death occurred in 24–48 hours following 5 mg kg.[23l]

At LD_{50} doses deaths are delayed in all species regardless of the route of administration, although gradations in severity of clinical symptoms have been observed. Anorexia and emaciation, variable leucopenia, and variable diarrhea have been observed in rabbits after skin application,[23j,36d] and after intravenous administration.[23k,n] Severe leucopenia was seen in rabbits receiving supra-LD_{50} doses, whereas only moderate transient leucopenia was observed at lower doses. Differential leucocyte counts in animals receiving sub-LD_{50} doses showed that the absolute numbers of lymphocytes were lowest on the second and third day with the greatest total reduction in granulocytes occurring on the same or following day.[23k,n] Essentially similar observations have been reported,[37c] but the absolute counts in this case have been reduced to 4,000 polymorphonuclear leucocytes and 6,500 lymphocytes for each rabbit. It has been concluded that small intravenous doses of HN1 repeated daily in the rabbit have, after an intermediate slight depression, a stimulatory effect on heterophilic polymorphonuclear leucocytes, and a mildly depressive effect on lymphocytes. In view of the complexity of the procedures, the original report should be consulted for details.[37d]

Rabbits gassed at LCt_{50} levels[23m,35c] and goats exposed to HN1 vapor under field conditions[32] showed no significant alteration in daily total and differential white cell counts. However, a terminal leucocytosis occurred in the rabbits and was possibly attributable to secondary pulmonary infection. A slight neutrophilic leucocytosis and a slight rise in hemoglobin (1 gram per cent) occurred in the goats. In rats exposed to an LCt_{50} dose, significant clinical

TABLE 4. Toxicity of HN1 for various species. (LD_{50} in mg kg.)

Animal \ Route	Cutaneous (free base)	Subcutaneous	Intravenous	Intraperitoneal	Oral
Mouse	13[23k]	§1.0,[31] 1.2,[23k] 1.45[35c]	.....	§1.05[35c]	.....
	.....	1.1[35c]	.....	1.03[37c]	.....
		*2.05[35c]	....	*1.80[35c]	.....
Rat	*17[27e]	§1.0[23k]	0.5[23k]	....	**2.5[35c]
Rabbit	[illegible] ca. 15 [illegible]	.....	ca. 2.0[23k,35c]	....	‡1.5<3.0[31]

* According earlier value LD_{50} = 11 mg kg.[23e]
† An LD_{50} is 20 mg kg.[23d]
‡ Fatalities 2/4 at 3.0 mg kg, and 3/4 at 1.5 mg kg.
§ Agent administered as the hydrochloride
Agent administered as the free base in mineral oil
* Agent administered as the free base in olive oil
** Agent administered as the free base in corn oil.

symptoms of systemic intoxication apart from weight loss failed to develop.

Neurologic Injury. In rats given LD_{50} and supra-LD_{50} doses intravenously, clinical symptoms were conspicuously absent, except for a late appearing diarrhea in some animals surviving beyond 70 hours. In the absence of the usual signs of systemic intoxication, noteworthy manifestations of neurologic injury appearing on the third or fourth day were observed. These consisted of increased irritability, and abnormalities of posture and movement, progressing in the severe cases to involvement of the vestibular and cochlear mechanisms. Usually death rapidly followed the onset of the extreme stage, and among survivors of less severe injury hyperirritability remained for weeks. This neurologic injury has been seen also after exposure to HN1 or HN2 vapor and after the intravenous administration of HN2, but never after cutaneous or subcutaneous administration of either agent.[11,23k,l] The clinical manifestations and the histopathologic lesions, particularly the extensive demyelinization of peripheral nerves seen in 1 3 animals examined, resemble those produced by vitamin B_1 deficiency. However, the rapid development of the syndrome following HN1 and HN2 equivocates the involvement of vitamin B_1 metabolism.

Rats injected subcutaneously with LD_{50} and sub-LD_{50} doses were notably free from clinical symptoms. Leucopenia was absent, weight loss slight, and diarrhea inconstant and mild, although enteritis (see pathology section) was severe.[23o]

One dog, succumbing on the fifth day following the cutaneous application of 10 mg kg of the free base of HN1 to the clipped shaved back, presented a clinical condition resembling shock which was entirely similar to that following the intravenous administration of HN2 and HN3 described later. However, there was no bloody diarrhea or extensive vomiting[56] such as were seen in the series of dogs injected intravenously.[11]

Apart from the above observations, few other clinical examinations have been made. An elevation of blood sugar of questionable specificity has been reported at 30 and 90 minutes after exposure of goats to HN1 vapor, with normal values again prevailing after 3 5 hours.[46] Alterations of the sedimentation rate were observed in rabbits following the intravenous administration of HN1.[57] In rabbits exposed to HN1 vapor, daily hemoglobin values did not vary significantly;[58] goats exposed under field conditions showed a slight rise.[32] In rats given HN1 intravenously there was no change in blood calcium. A marked thrombocytopenia occurred in severely intoxicated dogs after intravenous administration.[58] Other blood changes after HN1 intoxication are described in "Blood Studies" under H (Section 22.2.1). Adrenal analyses after HN1 are discussed under HN2, "Special Studies" (Section 22.5.1).

Prophylaxis and Therapy of Systemic Intoxication

Prophylactic and therapeutic studies have been concerned with the prevention of systemic intoxication by HN1 absorbed through the skin. In order to be effective and significantly to lower the mortality rate (3 6), extirpation of the contaminated skin must occur within 15 minutes after the application of 20 mg kg (LD_{50}) of the free base. The parenteral administration of $Na_2S_2O_3$ was markedly successful (mortality, 1 11) if given prophylactically 1 minute before similar exposures, but only erratic results obtained when $Na_2S_2O_3$ was given therapeutically.[56d]

Pharmacology of the Hydrolytic Derivatives of HN1

The toxicity of the transformation products and other derivatives of HN1 are shown in Table 5.

1-Ethyl-1-(β-chloroethyl)ethylenimonium chloride does not possess marked parasympathomimetic action. Large doses given intravenously to rabbits produced only mild transient salivation and no pupillary changes.[23k,26] It is not a central stimulant,[26] but causes depression when given intravenously or subcutaneously in mice and intravenously in rabbits.[23k] Large doses intravenously administered to rabbits induce severe muscular paralysis.[23i] Administered subcutaneously to mice and intravenously to rats at LD_{50} doses, this compound produced delayed deaths and its action was comparable to the parent amine with respect to weight loss, diarrhea, and the absence of leucopenia. Rats do not show the neurologic syndrome seen after intravenous doses of the parent amine.[23k] In the rabbit, the leucopenic action is no greater than and possibly less than that of the parent amine, but weight loss and diarrhea are observed.[23k,56]

Ethyl-β-chloroethyl-β-hydroxyethylamine (HN1 chlorohydrin) seems to produce qualitatively the same effects as the parent amine. Large doses given intravenously, subcutaneously, or intraperitoneally in mice produce symptoms ranging from tremors to convulsions accompanied by hyperirritability and

TABLE 5. Toxicity of transformation products and other derivatives of HN1. (LD_{50} in mg kg.)

Iv = intravenous injection.
Ip = intraperitoneal injection.
Sc = subcutaneous injection.

Substance	Remarks	Route	Animal	LD_{50}	Ref.
1-Ethyl-1-(β-chloroethyl)ethylenimonium salt	Pure pierylsulfonate dissolved in saline	Iv	Rabbit	ca. 3.0	23k
			Rat	0.5	23k
		Sc	Mouse	<2.0	23k
	A hydrolysate containing at 5 min by analysis 90% of the original amine in the form of the first chloroethylene imine	Iv	Rabbit	2-3	26i
Ethyl-β-chloroethyl-β-hydroxyethylamine	Pure pierylsulfonate dissolved in saline	Iv	Rabbit	5-10	23k
			Mouse	<8	23k
		Sc	Mouse	<8	23k
	Pure pierylsulfonate converted to hydrochloride	Ip	Mouse	ca. 10	20d
1-Ethyl-1-(β-hydroxyethyl)ethylenimonium salt	Pure pierylsulfonate dissolved in saline	Iv	Rabbit	ca. 5-6	23k
			Mouse	ca. 5	23k
		Sc	Mouse	ca. 5.5	23k
	Pure pierylsulfonate converted to the chloride	Ip	Mouse	7.0	20c
Ethyldiethanolamine (TL 596)	Free base, neat (nontoxic on repeated weekly administration)	Iv	Rabbit	>200	16c
		ip	Mouse	ca. 200	20c
Ethyl-*bis*(β-hydroxyethyl)methylammonium chloride	In saline	Ip	Mouse	ca. 75	20d
Ethyl-*bis*(β-chloroethyl)amine oxide (HN1 amine oxide)	In saline	Ip	Mouse	ca. 75	20h
Ethyl-β-chloroethyl-β-pyridiniumethylamine chloride hydrochloride	In saline	Ip	Mouse	ca. 200	20h
Ethyl-β-chloroethyl *bis*(β-hydroxyethyl) methylammoniumethylamine chloride hydrochloride					

incoordinated hyperactivity. At higher doses intravenously, gasping and momentary cessation of respiration occur. Lower intravenous doses (8-20 mg/kg) caused delayed deaths similar to those seen in rats given HN1·HCl intravenously. Lower subcutaneous doses (12-20 mg/kg) and intraperitoneal doses (40-50 mg/kg) produce mixed deaths, 50 per cent of the animals dying within 2 hours and the remainder in 2-5 days after suffering weakness, diarrhea, and weight loss. Still lower doses given intraperitoneally cause only delayed deaths.[23k]

In the rabbit higher doses caused depression, progressing until death between 12 and 16 hours in one instance (40 mg/kg), but in the second instance (20 mg/kg) depression was punctuated by a period of hyperexcitability and hyperactivity, possibly a release phenomenon. Rabbits survived 5 mg/kg and developed a mild leucopenia.[23k]

1-Ethyl-1-(β-hydroxyethyl)ethylenimonium chloride (HN1 hydroxy imine) given to mice intravenously, subcutaneously, or intraperitoneally at LD_{50} and supra-LD_{50} doses caused acute deaths, the animals progressing from depression to weakness and terminal respiratory convulsions. Given intraperitoneally, the compound caused a significant number of delayed deaths among mice surviving the acute toxic action.[23k] Administered intravenously in the rabbit, this compound produces depression and paralysis, death being due to paralysis of the respiratory muscles.[26i] The depression may last for 24 hours,[23k] the paralytic action is reversible, and survivors of the immediate period recover.[26i] This derivative possesses no parasympathomimetic or leucopenic action, and survivors show no weight loss.[23k, 26i]

22.1.2 Systemic Pathology of HN1 Intoxication

The systemic pathologic action of HN1 has been studied less than that of its homologs. Table 6 shows

the intensity of total systemic injury and of individual lesions following intoxication by LD_{50} doses administered by various routes.

At 0.5 LD_{50} doses the pattern of observations was not so constant. The ranking lesions were lymphoid atrophy after intravenous administration and gassing, and enteritis after subcutaneous administration and cutaneous application. Myeloid injury was the mildest lesion by any route. The severity of leucopenia at 0.5 LD_{50} doses relative to other lesions was a noteworthy observation and did not appear to parallel the damage to the lymphoid tissue or the bone marrow.[14,23a]

In rabbits given HN1·HCl intravenously, enteritis, lymphoid injury of varying severity, and moderate damage to the bone marrow have been observed, and the last lesion in this species parallels the leucopenia, except when recovery from leucopenia was in progress at the time of sacrifice.[23a] Following the skin application of HN1 in rabbits, lymphoid atrophy and enteritis are more severe than the bone marrow injury, the latter paralleling the leucopenia.[23j]

In the above pathologic studies no injury occurred to the upper alimentary canal, the oral cavity, pharynx, esophagus, and stomach being free of lesions following parenteral administration and cutaneous application (when ingestion was prevented). Following intubation of HN1·HCl in rabbits, constriction and congestion of the stomach was a frequent observation and one instance of hemorrhage in the duodenum was recorded.[31]

Judging from the rat series, it is questionable that the severity of enteritis, bone marrow injury, and lymphatic tissue damage is sufficient to account for death of the animals.[23a]

22.4.3 Some Observations on Human Intoxication

In men inadvertently exposed to HN1 vapor, the most prevalent symptoms were conjunctivitis, laryngitis, bronchitis, hoarseness, coughing, elevated temperature, nausea, and vomiting. Random total and differential white cell counts, in many instances lacking values in the critical period after exposure, showed no significant variation.[25] It is apparent that most of the clinical symptoms resulted from local irritation.

Conjunctivitis and acute asthmatoid bronchitis developing from exposure to minute quantities of HN1 vapor have been reported as an idiosyncrasy to this agent. At hospitalization, temperature, blood count, hemoglobin determination, and sedimentation rate were normal; the results of urine analysis were negative.[25]

22.5 METHYL *bis*(β-CHLOROETHYL)-AMINE (DICHLOR AMINE, HN2, 1130, TL 116, S)

22.5.1 Pharmacology

Toxicity

The toxicity of HN2 on administration by various routes is shown in Table 7. In addition to these data, the LD_{50} for HN2 intravenously administered to chickens is approximately 10 mg/kg.[23a] Intravenously administered to pigeons, 20 and 15 mg/kg killed 1/1, while 10 mg/kg killed 0/1.[23a] Rats tolerated a total of 138 subcutaneous injections of small doses of HN2·HCl during a period of 7 months, and developed an increase in resistance to the systemic effects of the HN2. Growth was negative during the injection period, and a mild progressive leucopenia was apparent, but there was no extreme depletion of the hematopoietic system. Seven rats given 0.4 mg/kg daily for 4 days showed, at the end of this course of repeated injections, weight loss and leucopenia comparable to that seen in previously untreated rats given 0.24 mg/kg per day.[23a]

The problem of contaminated drinking water involves the administration of aged solutions and, whether administered by intubation or allowed *ad libitum*, must concern the transformation products of HN2. Thus, the toxicity of aged solutions will be influenced by the time elapsed after contamination and by the concentration, pH, and buffering capacity of the solution (see Chapters 19 and 20). The pharmacologic properties of aged solutions are the summation of the properties of the individual transformation products whose existence is permitted by definition of these conditions. The discussion in this section of the properties of these transformation products makes gratuitous a discussion of the voluminous data on the properties of aged solutions. A review of the subject is available.[3]

One aspect of aged solutions may be briefly mentioned here. The designation SB has been given to substances arising in, and imparting unique pharmacologic properties to, aged solutions of HN2 and HN2 chlorohydrin. The SB which occurs in aged solutions of HN2 is methyl-β-chloroethyl-β-hydroxyethylamine, and the SB present in aged solutions of the chlorohydrin is 1-methyl-1-(β-hydroxyethyl)-

TABLE 6. Systemic effects in rats of LD_{50} doses of HN1.

These data are an average of data reported in detail.[1] The abbreviations iv, sc, cut, and gas represent respectively intravenous, subcutaneous, cutaneous application, and exposure of the whole body to the agent dispersed by atomization. Intravenously and subcutaneously, a solution of HN1·HCl in physiological saline was administered. The free base was applied to the skin.

Route	Lesion: Total systemic injury	Lymphoid atrophy	Myeloid injury	Leucopenia	Enteritis	Weight loss
Iv	Moderate	Moderate	Mild	Mild	Moderate	Severe
Sc	Mild	Moderate	Mild	Absent	Mild	Mild
Cut	Moderate	Moderate	Mild	Mild	Moderate	Severe
Gas	Mild	Moderate	Mild	Absent	Mild	Moderate

TABLE 7. Toxicity of HN2 for various species. (LD_{50} in mg/kg.)

Animal \ Route	Intravenous LD_{50}	Ref.	Subcutaneous LD_{50}	Remarks	Ref.	Cutaneous (free base) LD_{50}	Ref.	Oral LD_{50}	Remarks	Ref.
Mouse	ca. 2.0	23i	2.6		23e					
			2.8		120					
			2.9		102a	29	23k	20	Fed mice	23e
			3.3‖		16i	ca. 35*	16b	10	Fasted mice (18 hr)	23f
			ca. 4.0		72			10		73
			ca. 4–5	Free base in Nujol	117					
			4.5	Free base in peanut oil	120					
Rat	1.1	23e	1.9		23e	14	123f	10		73
			ca. 2.0**	Fresh solution of HCl in water	81	15	68	13–20	HCl in water	117
						15–18	105e	55–85	Free base in water	117
			3.0	Free base dissolved in tributyrin	68	22*	23e			
Rabbit	ca. 1.6	23q	3.0		74	12	68	12		73
	2.5‡	26g	3.0	Free base dissolved in tributyrin	68	ca. 15	23k	12.5–17.5	HCl in water	117
						ca. 17§	38	5	Free base dissolved in tributyrin	68
			ca. 4–5	Free base dissolved in Nujol	117					
Guinea pig			2.0	Free base dissolved in tributyrin	68					
			<5	Free base dissolved in peanut oil	119	>25	68	12		73
			ca. 4–5	Free base dissolved in Nujol	117					
Dog	1.0†	11, 23k								
Goat						20	6c	<100		73
Monkey						<50	123g			

* Amending earlier value, LD_{50} = 14 mg kg.[23k]
† LD_{50} 1.0 killed 13/20.
‡ LD_{50}.
§ This reference states that 33 mg is a lethal dose for a 2-kg rabbit.
‖ Amending earlier value, LD_{50} = 3.6 mg kg.[16b]
* Value estimated from data in reference cited.
** Amending earlier value, LD_{50} = 5 mg kg.[23]

ethylenimonium chloride.[20b,c] These substances account for the pharmacologic properties of the aged solution of HN2 and of the chlorohydrin.[23i]

PHARMACODYNAMICS

Cholinergic Action. The cholinergic action of HN2 is similar to the cholinergic action of injected acetylcholine, and thus shows muscarinic action on glands and smooth muscle (parasympathomimetic) and nicotinic action on autonomic ganglia and skeletal muscle. Parasympathetic effects have been observed following parenteral administration of the hydrochloride in various species,[23a,23f,g,73] and in rabbits following parenteral administration of the free base.[67] These parasympathetic effects do not originate centrally (i.e., by a release phenomenon) since salivation developed in dogs with denervated salivary glands.[73] In normal animals salivary responses were prevented

by prophylactic administration of effective doses of atropine.[26f,73,82] However, gastric and duodenal secretion in decapitated and decerebrated cats was only altered by such treatment and not prevented.[79] Atropine failed to abolish the salivary response once secretion had begun,[78,82] failed even to alter gastric and duodenal secretion in decapitated cats when given therapeutically,[79] and had no effect on survival.[23b,26f,i,82,78] Since atropine failed to act on salivation therapeutically, the site of the muscarinic action of HN2 would appear to be peripheral to the site of atropine action and may be located within the effector cell.

Cholinesterase inactivation by HN2 [105c] could lead to the accumulation of acetylcholine within the effector cells, but it has been emphasized [3] that the concentration of HN2 required to inhibit cholinesterase *in vitro* is greater than that required with other inhibitors, and that eserine itself potentiates the action of HN2.[26f,39,78] In addition, it is not clear that acetylcholine accumulates in spite of cholinesterase inactivation. For example, there was no accumulation of acetylcholine *in vitro* when brain tissue was incubated in saline containing eserine and HN2, although an accumulation occurred in the presence only of eserine. This circumstance gave rise to the suggestion that HN2 inactivates cholinacetylase as well as cholinesterase.[109] Nor does cholinesterase inhibition seem implicated *in vivo* since in the cat intoxicated with HN2 the arterial blood pressure does not fall on stimulation of the peripheral end of the cut chorda lingual nerve, whereas such stimulation produced a fall in the eserinized cat.[109]

The isolated gut of the rabbit, cat, and rat was reversibly stimulated at low concentrations in Tyrode's solution, the stimulation being blocked by previous treatment by atropine.[23a,39,74] Above a concentration of 200 mg l there was an initial stimulation followed by depression which soon became irreversible by washing.[23a]

The behavior of blood pressure following HN2 administration is attributable to muscarinic and nicotinic actions. In the anesthetized animal, blood pressure fell (muscarinic action) following administration of HN2, and in the atropinized anesthetized animal a rise (nicotinic action) in blood pressure occurred.[5,8,78] In spite of symptomatic control of the immediate effects, the animals failed to recover from the anesthetic and died of respiratory failure with blood pressure at shock levels.[26f]

HN2·HCl at a concentration of 40 mg l had no direct contractile action on the isolated frog's *rectus abdominus* but augmented the contraction produced by small doses of acetylcholine. This eserine-like effect was reversible by washing. A concentration of 200 mg l caused a direct stimulation, in addition to augmenting the effect of acetylcholine.[78] HN2 free base applied directly to the intact heart of the pithed frog increased the heart rate. Applied directly to the sciatic nerve of a frog, it did not block motor impulses in the area of contamination. Injected into, or applied directly to, the gastrocnemius muscle of the frog it produced contraction.[42]

Central Action. In unanesthetized animals central excitation is manifest at high doses but this factor is different from the immediate, direct, intense convulsive action of HN3. Unsustained convulsions of varying character have been seen only after large doses given intravenously in rabbits,[23a,26f,g,42] and never after cutaneous or subcutaneous administration.[26f,g]

Paralytic Action. The most significant pharmacologic property of HN2 in large doses is its paralytic action. Within 10 15 minutes after intravenous injection a progressively increasing skeletal muscle weakness appears, becoming evident first in the muscles of the head and neck and then in the muscles of the extremities and thorax.[23a,26f,g] This paralytic action has been compared to paralysis by nicotine [26f] and curare.[26g] Comparable to the latter, a 6.4×10^{-4} *M* solution of the HN2 approximately 1 minute old at *p*H 7.4 caused a rapid inhibition of transmission across the myoneural junction of the frog's sartorius muscle-nerve preparation, the inhibition being reversible up to 30 minutes. HN2 was without effect upon the excitability of the nerve or muscle, but caused a slow progressive reduction in contractility which was irreversible and continued after exposure.[23] The contractility of the isolated frog sartorii decreased steadily, and a complete loss of irritability to direct electrical stimulation was observed after an exposure of 80 minutes to 0.01 *M* HN2.[15]

Comparable to the action of nicotine, respiration in the anesthetized dog was initially stimulated for 1 or 2 minutes; then some minutes later a larger and more prolonged stimulation appeared, lasted 10 15 minutes, and was followed in one case by depressed respiration and death 15 minutes later. Stimulation of respiration is presumably a specific property of nicotine as compared with curare, and serves as a major difference in the action of these compounds.[13a]

Death in rabbits treated intravenously with 20 mg/kg or more occurs in 30 minutes to 4 hours, and has been attributed to respiratory failure.[23a,26f,x]

Paresis of the lower extremities, proceeding to flaccid paralysis before death has been observed in two monkeys, one receiving 100 mg/kg, the other receiving 50 mg/kg of HN2 free base on the skin.[123x]

Delayed Deaths. The symptomatology of delayed deaths in the smaller laboratory animals following intoxication with HN2 and HN3 has been reviewed.[3] The syndrome is characterized by failure to eat and drink, emaciation, muscular weakness and debilitation, watery diarrhea, loss of body temperature control, and eventual impairment of respiration.[3]

In dogs intoxicated with 1 mg/kg of HN2·HCl intravenously, vomiting began within a few hours after intoxication, increasing in severity and generally continuing accompanied by anorexia through the second and third day. Vomiting, both early and late, may reflect a neurogenic (or perhaps paralytic) disturbance later associated with intestinal injury. Profuse salivation was sometimes but not invariably present. Diarrhea, usually blood-stained or frankly hemorrhagic, was generally present on the second to fourth days.[11]

As a result of profuse vomiting and diarrhea, there was loss of fluid, electrolyte, and protein as revealed by the following biochemical data: (1) reduction in volume of both extracellular fluid and circulating plasma volume; (2) reduction in plasma chloride concentration; (3) rise in carbon dioxide capacity and blood *p*H; (4) reduction of total circulating plasma protein (probably a result of loss of protein in the diarrhea); (5) rise in concentration of plasma protein (the result of a greater loss of plasma water than protein); (6) a variable reduction in total circulating red cell volume which may be accounted for (a) by loss of cells through intestinal hemorrhage, or (b) by *in vivo* sequestration or trapping of cells; (7) variable rise in hematocrit (not necessarily proportionate to the reduction of plasma volume in the presence of cell loss or change in cell size); and (8) variable rise in hemoglobin (or oxygen capacity).[11]

Failure of oxygen capacity to rise as markedly as would be expected from the rise in plasma protein concentration suggested the loss of hemoglobin or red cells from the circulation or transfer of plasma water into the cells. Loss of body weight resulted from excessive fluid and protein loss and is more extensive than that due to starvation alone.[11]

Terminal weakness and coma, preceding death, occurred in the majority of dogs in the third to fifth day after intoxication. They were associated with low mean femoral arterial blood pressure, marked oxygen unsaturation of jugular blood (with presumably normal arterial oxygen saturation), reduction in body temperature, coldness of extremities, relaxation of the anal sphincter, and respiratory failure.[11]

Excluding a few animals with severe pulmonary injury or infection as a complication, it is inferred that death is caused by anoxia of the respiratory centers due to peripheral circulatory failure brought on by either (1) a reduction in blood volume attributable to loss of proteins, electrolyte, and water through vomiting and diarrhea, supplemented by loss of red cells through as yet unidentified channels, or (2) undescribed changes contributory to a fatal effect. No support is obtained for the theory that terminal circulatory collapse is due to exhaustion of either the heart or arteriolar bed, in consequence of prolonged bombardment by humoral vasoconstrictor agents. Despite terminal coma and hypotension, intoxicated dogs retained cardiovascular responsiveness to adrenalin given intravenously.[11]

Neurologic Injury. In Section 22.4.1 dealing with HN1, it was stated that neurologic injury occurs in rodents intoxicated with HN2 at LD_{50} or supra-LD_{50} levels after gassing and intravenous administration. The reader is referred to that section for a description of neurologic injury.

Other Observations. Blood studies, exclusive of those concerned with the leucocytes, have not been informative,[x,11,26,40,57a,58,67,68,74,123x] although the frequent suggestion of hemoconcentration is possibly significant. A marked thrombocytopenia has been reported.[58] Some blood changes have been previously described.

Electrocardiograph records of rabbits receiving 1–2 LD_{50} doses of HN2·HCl intravenously remained essentially normal until a short time before death and revealed no impairment of the excitatory or conductor systems of the heart.[23b]

The chief renal action, highly variable in relation to dose, is depression of tubular excretory function, a depression rapidly effected by 2–3 LD_{50} doses given intravenously in rabbits. Smaller doses caused a progressive impairment which became maximal in 5–10 days and resolved slowly. It was not demonstrated whether the tubular injury is a delayed result of a direct toxic action or secondary to injury of other organs. The rate of glomerular filtration was not

consistently affected, being reduced only under conditions where circulatory inadequacy may have been present. As judged by the rare occurrence of proteinuria, there was no specific injury of the glomerular membranes.[2] Blood gas analyses indicate that intravenous administration of HN2·HCl did not cause serious pulmonary injury in rabbits.[11,23k]

Pharmacology of Transformation Products of HN2

The toxicity of the transformation products and certain other derivatives of HN2 is shown in Table 8.

A hydrolyzed solution of HN2 containing by analysis 90 per cent of the parent amine as 1-methyl-1-(β-chloroethyl)ethylenimonium chloride (I) possesses pharmacologic properties similar to those of the parent amine. Parasympathetic effects were observed immediately in rabbits given 1·2 mg kg intravenously, and were blocked by atropine. Large doses gave immediate prostration and death. This solution possessed no central excitatory action, but produced typical muscular paralysis, and in large doses was possibly a medullary depressant.[23j]

Immediately following the intracarotid injection of 1 mg kg of this solution in the dog, there was a stimulation of respiration, the promptness of which suggested stimulation of the chemoreceptors in the carotid sinus. Miosis was not prominent at any time, but during the injection a marked bradycardia was observed. The salivary response, beginning shortly after the injection, was more marked in the ipsilateral than in the contralateral glands. Dogs given the compound intravenously showed similar responses after a latent period, with the exception that salivation was bilateral. With respect to the onset, duration, and extent of vomiting, little difference was observed between animals receiving intravenous and those receiving intracarotid injections. Unilateral edema was observed within a few hours in tissues receiving arterial blood from branches of the carotid peripheral to the site of injection. Death at 18 hours in one dog was attributed to asphyxia as a result of marked edema of the glottis. The remaining dog developed bloody diarrhea, had a clonic convulsion 74 hours after injection, and died in 86 hours.[23a]

Dogs given 0.5 mg kg of the hydrolyzed material presented a similar appearance. One dog was sacrificed at 5 days after a clonic-tonic convulsion which left the animal weak and moribund. The brain from this dog and one from a fatality showed no damage on the surface of the intact brain or incut sections. Histologically, there were small areas of focal necrosis scattered throughout the cerebral lobe, but significant evidence of vascular damage or hemorrhage were not associated with this lesion. No cerebellar damage was noted.[23j]

Mice given large doses of 1-methyl-1-(β-chloroethyl)ethylenimonium picrylsulfonate (II) intravenously or subcutaneously showed parasympathetic effects, depression, weakness, and death in from 1 minute to 12 hours, depending on the dose and route. Doses (expressed in terms of the hydrochloride) of 2.0 mg kg intravenously and 2.4 mg kg subcutaneously cause delayed deaths.[23i] Leucopenia is a constant observation in animals given lethal doses of II.[23i,26i,74]

A $3.4 \times 10^{-4}M$ solution of II 1 minute old at *p*H 7.3 reversibly blocked myoneural transmission in the frog's sartorius muscle-nerve preparation. This solution had no effect on excitability of the nerve or muscle, but unlike the parent amine, loss of contractility was delayed.[23j]

Methyl-β-chloroethyl-β-hydroxyethylamine hydrochloride (III) given parenterally to mice gave rise after a latent period to depression, followed in 1 or 2 hours by terminal respiratory convulsions and death. Survivors of the immediate effects showed no evidence of systemic intoxication and no delayed deaths were observed. The intravenous and intraperitoneal toxicities are lower than the subcutaneous, suggesting that the toxic effects of this compound are propagated through 1-methyl-1-(β-hydroxyethyl)-ethylenimonium chloride (IV), since subcutaneous administration provides conditions favorable to the formation of the latter compound.[23i] In rabbits large doses given intravenously produce depression, severe muscular paralysis, and early deaths. At lower doses, paralysis is reversible.[23i,26i] Compound III does not give rise to leucopenia.[23i,26i,74]

Prophylaxis with Nembutal, urethane, hexamethylenetetramine, and sodium thiosulfate protected rabbits against lethal doses of III. The action of Nembutal seemed distinct from the other agents in that it was effective in low doses, 7.5 mg kg of Nembutal affording some degree of protection against an approximate 2.5 LD_{50} dose of III. It was suggested that this distinction might be the result of a covering or "lytic" action at specific loci. No antidotal value obtains when Nembutal is given therapeutically, or when anesthetic doses of magnesium sulfate are given prophylactically. Occlusion of the carotid arteries in unanesthetized rabbits during and for 15 minutes

TABLE 8. Toxicity of transformation products and other derivatives of HN2 (LD_{50} in mg/kg.)

Ic = intracarotid injection
Sc = subcutaneous injection
Iv = intravenous injection
Ip = intraperitoneal injection

Substance	Method of obtaining desired substance and other remarks	Route	Animal	LD_{50}	Ref.
1-Methyl-1-(β-chloroethyl)ethylenimonium salt	Pure picrylsulfonate dissolved in saline.	Sc	Mouse	2.1	23i
		Iv	Mouse	ca. 1.5	23i
	A 45-min hydrolysate containing by chemical analysis 90% of the parent amine as the desired product.	Iv	Rabbit	1.0–3.0	26i
		Sc	Rabbit	1.0	74
		Iv	Dog	ca. 0.50	55d
		Ic	Dog	ca. 0.25	55d
Methyl-β-chloroethyl-β-hydroxyethylamine	Pure hydrochloride	Sc	Mouse	16	23i
				15.7	10h
				10	72
			Rat	20	72
			Rabbit	ca. 10	74
		Iv	Mouse	22.5	23i
			Rabbit	ca. 12.0	23i
		Ip	Mouse	34.0	23i
		Oral	Mouse	25	72
			Rat	80	72
	A sample containing 60% of the desired product by analysis.	Iv	Rabbit	30*	26i
Methyl-β-acetoxyethyl-β-chloroethylamine†	Pure synthetic product	Sc	Mouse	20	71
		Iv	Mouse	>36	23y
		Sc	Mouse	>500‡	57a
Methyl-*bis*(β-acetoxyethyl)amine	Water	Iv	Mouse	4.2	23i
1-Methyl-1-(β-hydroxyethyl)ethylenimonium salt	Pure picrylsulfonate dissolved in saline.		Rabbit	3–5	23i
		Ip	Mouse	7.5	23i
	A 20-hr hydrolysate containing by analysis 60% of the original amine as the desired product.	Iv	Rabbit	ca. 10	26i
Methylethanolamine		Iv	Rabbit	>200	16e
Bunte salt of HN2	Saline. Not leucotoxic at LD_{50}.	Sc	Mouse	>500	23f
		Iv	Mouse	>200	22f
			Rabbit	>50	23f
Methyl-*bis*(β-dithiocyanatoethyl)amine hydrochloride	Immediate deaths	Sc	Mouse	ca. 20‡	16i
Methyl-β-chloroethyl-β-pyridiniumethylamine chloride hydrochloride	Saline	Ip	Mouse	ca. 100	
Methyl-β-chloroethyl-*bis*(β-hydroxyethyl)-methylammoniumethylamine chloride hydrochloride	Saline	Ip	Mouse	ca. 350	20g
		Sc	Mouse	>80‡	16g
Methyl-*bis*[*bis*(β-hydroxyethyl)methylammoniumethyl]amine dichloride	Saline	Ip	Mouse	ca. 1,200	20e
Methyl-β-hydroxyethyl-*bis*(β-hydroxyethyl)-methylammoniumethylamine chloride hydrochloride	Saline	Ip	Mouse	ca. 1,500	20h
N,N'-Dimethyl-N,N'-*bis*(β-chloroethyl)piperazinium dichloride	Saline. Not leucotoxic at LD_{50}.[23f]	Sc	Mouse	ca. 500	23a
Methyl-*bis*(β-chloroethyl)amine oxide (HN2 amine oxide)	Saline	Sc	Mouse	>80	16i
		Ip	Mouse	ca. 100	20e

* These investigators give 30 mg/kg as the lethal dose of a sample containing 60 per cent chlorohydrin, and this value is reducible presumably to 18 mg/kg of the pure compound (30 × 0.6 = 18).

† Conversion of methyl-β-acetoxyethyl-β-chloroethylamine to the quaternary methiodide is reflected in a decrease in toxicity. On subcutaneous injection in mice, 250 mg/kg gave no deaths and doses of 500 and 1,000 mg/kg each killed 2/2 animals.

‡ Two animals studied with each dose.

after the intravenous administration of supra-LD_{50} doses of III affords some protection, but is less effective than Nembutal.[23a]

The acetate ester of III, methyl-β-acetoxyethyl-β-chloroethylamine, caused salivation and diarrhea within a few minutes after subcutaneous injection in

mice. This immediate effect was followed by a period in which the animals showed partial paralysis, incoordination, and tremors. Death accompanied by terminal convulsions occurred in a short time.[71]

1-Methyl-1-(β-hydroxyethyl)ethylenimonium picrylsulfonate (V) on parenteral administration in rabbits and mice possessed essentially the same pharmacologic properties as the chlorohydrin.[231] Following the intravenous administration of a hydrolyzed solution of HN2, 60 per cent in the form of IV, the leucopenia and slight parasympathomimetic action were attributed to the presence of small amounts of I.[231] Otherwise, the pharmacologic properties of this solution agree with those of the pure picrylsulfonate (V).

Both III and V block myoneural transmission in the frog's sartorius-nerve preparation with some reversibility. Unlike the parent amine and II, the former compounds slowly impair the excitability of both the nerve and muscle and completely lack the effect on contractility.[231]

Prevention of Systemic Effects of HN2

Sodium thiosulfate, which reacts chemically with HN2, prevents systemic injury if given in doses adequate to yield relatively high blood levels. The subcutaneous administration of 0.5 g kg of a 5 per cent solution of sodium thiosulfate 20 minutes before, combined with the intravenous administration of 0.5 g kg of a 25 per cent solution 5 minutes before, the subcutaneous administration of 40 mg kg of HN2, prevented the parasympathetic effects and increased survival time from 2 to 20 hours. Animals similarly treated prophylactically may survive indefinitely after 20 mg kg subcutaneously, although they showed a transient leucopenia. Control animals receiving 10 mg kg subcutaneously survived only 6 hours, whereas those pretreated as above with sodium thiosulfate survived indefinitely and showed only a transient leucopenia. The protection against 5 mg kg was almost complete. Similar protection has been shown against small subcutaneous doses repeated daily when sodium thiosulfate is given at the same time but in a different site. This prophylactic procedure modified to provide sodium thiosulfate over longer periods was effective against an LD_{50} dose of HN2 applied to the skin.[28c]

Protection against intravenous administration of HN2·HCl is less striking. Sodium thiosulfate prevented the parasympathetic effects and protected against the paralytic action, but not against leucopenia or central excitation, the intensity of the convulsive phenomena being aggravated.[28a]

Thiosulfate treatment protected against the acute prostration, the parasympathomimetic action, and the rapidly developing paralysis induced by a 30-minute hydrolysate of HN2. The animals survived several days and showed no leucopenia, but eventually died with a late unexplained paralysis. The protection against the rapidly lethal effect of 20 mg/kg of 60- and 120-minute hydrolysates was found to be complete.[28a]

A blood level of 75–125 mg per cent initiated prophylactically and maintained by repeated administration of sodium thiosulfate protected against 7 hourly intravenous doses of 1 mg/kg of 1-methyl-1-(β-chloroethyl)ethylenimonium chloride (as a 45-minute hydrolysate). This prophylactic procedure is equally effective against topical applications of HN2. Initiated up to 15 minutes after the skin application, the treatment is also of great value, but when initiated after 30 minutes, the course in such animals is similar to untreated controls.[28i]

Hexamethylenetetramine (HMT) likewise affords some protective action when given in adequate doses prior to the administration of HN2. The lethal effects of 16 mg/kg of HN2 applied to the skin of rats under Nembutal anesthesia were materially reduced by the parenteral administration of 5–8 mg kg of HMT. This treatment was initiated by the intravenous injection of 1 g/kg 1 minute before the HN2 and sustained by repeated subcutaneous injections. Delay in treatment until 15 or 30 minutes after the HN2 application lessened the efficacy.[27c] Infiltration with HMT of the subcutaneous tissues surrounding and beneath an area of skin contamination decreases the lethal effects of 16 mg/kg of HN2. However, specificity of HMT in this respect is somewhat obscured by the fact that a significant reduction in mortality occurred when saline was used for infiltration.[27c]

Single intubations with HMT in doses ranging from 0.5–3.0 g kg 30 or 60 minutes before placing 20 mg kg of HN2 on the shaved back of fasted rats (under Nembutal anesthesia) gave a significant reduction in mortality rate. Plasma samples taken 30–60 minutes following the HMT showed a concentration above 50 [illegible]per cent.[27d] Rats fed diets containing 10 per cent HMT over long periods were not protected against the systemic toxicity of HN2 absorbed through the skin nor were the skin burns diminished in intensity.[27c] Intubation with HMT be-

fore the skin application of 12 mg kg of HN2 reduced the tolerance of rats to a second dose of 20 mg/kg of HN2 given 10 weeks later, as compared with control rats receiving no HMT but otherwise given the same treatment.[27c]

In dogs, fluid replacement beginning at the time of intoxication and continued during critical illness apparently reduced the toxicity of an LD_{50} dose of HN2·HCl given intravenously. Glucose and sodium lactate did not seem to be an improvement over saline alone. When intravenous saline or saline in glucose was instituted in extremely ill and comatose animals, dramatic recovery from deep coma was sometimes achieved. Other therapeutic agents (amino acids, glucose, vitamin B complex, etc.) were given preliminary tests without success.[11]

Therapeutic measures specifically concerned with alleviation or correction of leucopenia have met with no better success than therapy of other systemic injuries. The administration of the leucocytosis-promoting factor of Menkin following the subcutaneous intoxication of goats [30] and the intravenous intoxication of dogs [29] was without effect. In the dog, two injections of the leucocytosis-promoting factor 48 and 84 hours before giving HN2 prevented granulocytopenia but not lymphopenia (total count at sacrifice was 25,000 cells/mm³ and consisted of 99 per cent neutrophils). At the time of sacrifice the bone marrow showed marked hyperplasia. In 2 rabbits intoxicated intravenously with 2 mg/kg of HN2·HCl, the intravenous injection at the lowest point in the leucopenic stage of enough exudate leucocytes to raise the count to approximately 10,000 mm³ neither hastened nor retarded the effects of HN2 (death occurred within 48 hours).[29] Whole blood transfusions given in volumes of 10 and 20 ml two times daily failed to alleviate (and possibly accentuated) leucopenia in rabbits given 2 mg/kg of HN2·HCl subcutaneously. The mortality rate was increased in these animals as compared to the controls, and this procedure possibly overloads the circulation and thus induces cardiac failure.[28]

Leucopenia in rabbits and goats intoxicated by HN2 was not prevented by the following substances: *p*-chloroxylenol in methylacetamide, sodium succinate, sodium fumarate, and sodium tartrate.[29] Liver extract, pentnucleotide, liver extract and pentnucleotide, methenamine, and thyrotropin failed to produce any alleviation of the hematologic changes following the skin application of an LD_{50} dose of HN2 to rabbits, although liver extract at the rate of 2 or 5 units (1 unit was insufficient) per day gave a slight reduction in mortality rate.[41]

Special Studies

In rats HN2·HCl produces effects similar in many respects to the alarm reaction described by Selye.[142] However, the late-appearing granulocytopenia, bone marrow injury, and diarrhea are not seen in the alarm reaction. Adrenalectomy increased the sensitivity of rats to HN2, causing earlier death (48-60 hours) and exaggerating the intestinal lesions.[23f] According to Selye, adrenalectomy has the same effect in respect to the alarm reaction. However, contrary to his statement that the lymphoid tissue does not atrophy in adrenalectomized rats, atrophic changes were found. Allowing for the short interval before death, these changes were of the same order of magnitude as those seen in sham-operated intoxicated animals.[23f,38] A marked adrenal hypertrophy has been noted in the rat after intravenous injection of all agents. This hypertrophy was due chiefly to an increase in water content, although increased adrenal nitrogen per gram of body weight accounted for some. No change in the concentration of ascorbic acid occurred. Total cholesterol concentration decreased and the per cent of free cholesterol showed a marked increase. Adrenal phospholipids increased, particularly after HN2 and HN3. Total lipids decreased.

Although the above changes are concomitants of intoxication by the β-chloroethyl vesicants, they are also seen during the first few days after severe thermal injury. The same is true for the changes in the electrophoretic pattern of plasma in dogs and the increase in plasma cholesterol and fibrin in dogs and rats (described elsewhere in this chapter), and the above change in the partition of cholesterol in the adrenals of rats, for all these changes have been noted after scalding or freezing the skin, exposure to X rays, physical trauma, or intradermal injections of turpentine.[38]

Occlusion of the blood supply to the legs of rats during and for 15 minutes after the intravenous injection of a 1.6 LD_{50} dose of HN2·HCl protected the femoral marrow, whereas the sternal and humeral marrow became aplastic.[23e] Temporary occlusion of the abdominal aorta and inferior vena cava during and shortly after the intravenous injection of HN2·HCl prevented the development of granulocytopenia and protected the femoral bone marrow in rabbits.[23e] When the blood supply to the small intestine of rats was occluded during and for 15 minutes after the

intravenous injection of HN2·HCl, the intestinal epithelium of the treated areas was uninjured, whereas the remainder of the gut showed alterations characteristic of HN2 intoxication.[28a] Cholinesterase in the kidney has been protected against inactivation by clamping the renal vessels during and for 15 minutes following the intravenous injection of 15 mg/kg of HN2.[15] Ligation of the common bile duct in rats prior to the subcutaneous injection of HN2·HCl did not prevent the intestinal lesion, thus demonstrating that these are not a result of the biliary secretion of the compound.[28c]

The serum of rabbits intoxicated with 1.5 LD_{50} of HN2·HCl became more favorable for the growth of hemolytic streptococci, this effect first appearing about 4–8 hours after injection. Heating the serum to 65°C for 30 minutes appeared further to enhance this growth-promoting property.[28i]

22.5.2 Systemic Pathology of HN2 Intoxication

The sequence of events after LD_{50} doses of HN2 consists of a relatively asymptomatic period of 1–2 days. During this time lymphatic injury is abrupt; the thymus, spleen, and lymph nodes involute rapidly, showing karyorrhexis, some karyolysis of the lymphocytes and a depletion of these cells, phagocytosis of the debris, and a persistence and proliferation of the epitheloid cells.[4, 6,16a,28b,c,d,28f,21] The hematopoietic cells of the bone marrow show injury, evidenced by changes in the staining reaction, vesiculation, and fragmentation of nuclei, and nuclear alterations in the megakaryocytes.[4, 6,28f,29,67,91] The epithelium of the small intestine shows vacuolization and nuclear swelling.[6]

Following this period, anorexia, weight loss, and mucoid diarrhea ensue, and finally prostration and death occur. During this time lymphatic atrophy persists. The hematopoietic cells of the marrow disappear uniformly and the marrow becomes aplastic, consisting of dilated sinusoids, fat cells, protein-rich fluids with a scattering of surviving cells including megakaryocytes, reticular, and endosteal cells. The peripheral blood is severely leucopenic, due to a progressive fall in granulocytes. The red count falls slightly but reticulocytes disappear, and it is evident that the production of hematopoietic cells has ceased. The small intestine is distended with fluid, and gastric stasis, possibly attributable to pyloric spasm, is consistently present in small animals. From the pyloris to the cecum, the small intestine shows inflammatory and degenerative changes with hyperemia, edema of the villi, sloughing of the epithelium, and metaplastic changes in the persisting and regenerating epithelium.[6]

Animals surviving LD_{50} doses gradually recover weight and show restoration of bone marrow and lymphoid tissue and a return of leucocytes in the peripheral blood. The lymphocytes return rapidly, the granulocytes more slowly, and, as seen in the rabbit, recovery is characterized by a shift to the left in the appearance of pseudoeosinophilic polymorphonuclear leucocytes containing basophilic granulations, macropolycytes, agranular polycytes, basophils, and occasionally abnormal red cells.[29] The diarrhea subsides and the intestinal epithelium is restored to normal.[6]

Other animals show similar restoration of the bone marrow and leucocyte count, but continue to lose weight, with or without obvious secondary infection, and die at a remote period. These deaths do not appear to be directly related to the primary effects of HN2.

In mice, rats, and rabbits gassed at $LC(Ct)_{50}$ concentrations, most of the vapor is absorbed in the upper respiratory tract [75] and lung damage is minimal.[6] Sufficient agent is absorbed from these sites to induce systemic intoxication as evidenced by hematologic and morphologic changes and by the occurrence of delayed deaths.

When the hydrochloride is given orally, injury to the duodenal and jejunal mucosa with ulceration, hemorrhage, and sometimes perforation occur;[28b] squamous metaplasia of the intestinal epithelium is a feature of healing. Presence of food in the gastrointestinal tract appears to exert a local protective action. Systemic intoxication can result from absorption of the agent from the intestinal tract.[6]

Comparison of the delayed systemic effects of HN2 with other leucopenic agents (e.g., benzene and X rays) show that it is remarkably similar to X rays (including the enterotoxic action), whereas the parallel to benzene is less evident.[6]

In rats, HN2 produces more severe total systemic injury than the other β-chloroethyl vesicants. Table 9 shows the intensity of total systemic injury and of individual lesions in rats given LD_{50} doses by various routes.

At sub-LD_{50} doses these lesions are usually reduced in severity, but on subcutaneous administration, moderate weight loss, myeloid injury, and leucopenia coupled with mild enteritis and lymphoid atrophy

TABLE 9. Systemic effects in rats of LD_{50} doses of HN2.

These data are an average of data reported in detail.[14] The abbreviations iv, sc, cut, and gas represent, respectively, intravenous, subcutaneous, and cutaneous application, and exposure of the whole body to the agent dispersed by atomization. Intravenously and subcutaneously, a solution of HN2·HCl in physiological saline was administered. The free base was applied to the skin.

Route	Lesion	Total systemic injury	Lymphoid atrophy	Myeloid injury	Leucopenia	Enteritis	Weight loss
Iv		Moderate	Moderate	Mild	Moderate	Absent	Severe
Sc		Moderate	Moderate	Mild	Severe	Severe	Moderate
Cut		Moderate	Severe	Moderate	Moderate	Severe	Severe
Gas		Moderate	Moderate	Moderate	Absent	Moderate	Severe

yield a total systemic injury which is only slightly less than that seen at LD_{50} doses.[14]

In a small series of rabbits, systemic injury was equally severe after cutaneous application and intravenous administration. After cutaneous application, lymphoid atrophy and bone marrow injury were moderate, leucopenia severe, enteritis mild, and weight loss very mild. After intravenous administration, moderate bone marrow injury, mild lymphoid atrophy, severe leucopenia, moderate enteritis, and mild weight loss were seen.[23].[a]

Other lesions typical of systemic action are not generally found. Congestion and edema in the lungs and gross congestion and hemorrhage in the trachea and larynx have been seen in animals given large subcutaneous doses of a solution of HN2 free base in tributyrin.[68] Massive pulmonary edema occurs in guinea pigs dying within 24 hours after receiving 5 mg kg of HN2 dissolved in peanut oil subcutaneously. The same dose given intraperitoneally does not cause pulmonary edema.[19] Moderate interacinar fibrosis in the pancreas together with edema and some nonsuppurative inflammation has been seen in cats 10 days after initiating 4 daily intubations of 5 mg kg HN2·HCl in water.[26b] In monkeys given 50–100 mg kg of HN2 on the skin, the outstanding pathologic lesions, apart from the local pathology, were confined to the lymphatic tissues, which had almost disappeared.[123a]

A few observations made on the central nervous system have shown that lesions are difficult to demonstrate even when severe functional derangement has occurred. After moderately large doses of HN2, disintegration of the neuronal elements and of the interstitial myelin are observable in the lenticular, thalamic, and hypothalamic nuclei. Lesions of lesser grade are detectable in the caudate nuclei. The cerebral cortex, pons, cerebellum, medulla, and spinal cord are unaffected. The blood vessels in the involved regions are not primarily injured although smaller vessels of capillary size are frequently ruptured and give rise to petechiae.[26f] In monkeys receiving 50–100 mg kg of HN2 on the skin, coarse eosinophilic granulations in the cells composing the basal ganglia were the only lesions observed in the tissues of the central nervous system.[123a]

LEUCOTOXIC ACTION

The leucotoxic action of HN2 was first reported in gassed mice.[16a] In most animals intoxicated by any route there is an early transient leucocytosis which may or may not be observed if counts are done at 24-hour intervals.[3–6,26g,38,57a,68,91,123a] This leucocytosis is due entirely to an increase in granulocytes, since the lymphocyte count begins to fall almost immediately after injection. It has been reported that the eosinophil count falls as rapidly as the lymphocyte count.[91] In dogs under Nembutal anesthesia with the thoracic duct cannulated, the lymph output during the first 5 hours was at first increased and then decreased, whereas the lymphocyte content of the lymph decreased. This circumstance resulted in a normal lymphocyte output during this period. One, two, and three days after intoxication lymph flow was only one-half normal and the cell count per cubic millimeter was very much less than normal. Since the decrease in circulating lymphocytes was greater than the decrease in output of lymphocytes, it was concluded that there was an increased disappearance of lymphocytes from the blood in some unexplained fashion.[91] However, this conclusion should be weighed against the known short life of circulating lymphocytes.[138]

The total leucocyte count begins to fall between 24 and 48 hours, reflecting the beginning decrease in circulating granulocytes. In rabbits, the animals most studied, and in mice, this granulocytopenia culminated usually in 3–4 days, at which time the total leucocyte count approached zero after LD_{50} doses, and few remaining granulocytes showing increased

maturity. In the dog there is a suggestion that the fall in the granulocytes is slower. Animals given 2 mg/kg intravenously died at a time when the granulocyte count was relatively high, although there was almost complete depletion of myeloid tissue at death. This circumstance was attributed to the longer life cycle of the canine granulocyte.[29] This delayed granulocytopenia seems confirmed in dogs receiving 1 mg/kg intravenously,[11] but in dogs given 1, 2, and 3 mg/kg subcutaneously it is stated that granulocytopenia appears *pari passu* with bone marrow injury, and that the granulocyte counts reached low levels in 3 days.[91]

It has been concluded that small intravenous doses of HN2 repeated daily in the rabbit have, after an intermediate slight depression, a stimulatory effect on heterophilic polymorphonuclear leucocytes, and a mildly depressive effect on lymphocytes. In view of the complexity of the procedures the original report should be consulted for details.[87d]

In animals surviving the culmination of hematopoietic injury, regeneration is delayed for several more days. Meanwhile, hematopoietic centers in other organs, notably the liver, show marked evidence of stimulation, so that even in animals dying between the fourth and seventh days some restoration of the leucocyte count may occur prior to death. Rabbits given 3 mg/kg intravenously and surviving longer than 100 hours had "toxic" pseudoeosinophils, anisocytosis, macrocytosis, and polychromasia.[6] In surviving animals the lymphocytes appear to recover before the granulocytes; histologically, marked hyperplasia in the thymus and lymph nodes parallels this recovery. Granulocytic recovery is spectacular in the blood, the white blood cell count rising from leucopenic to normal, or even supranormal levels almost overnight. This phenomenon appears to be related to the outpouring of immature granulocytes, and regenerative activity may persist for 2–3 weeks. (In some rabbits recovery from the initial leucopenia may be followed by a second period of leucopenia.[87e]) In mice, a species particularly sensitive to overstimulation of the leucopoietic tissue, hyperplastic foci having the dimensions and intensity of a leucemoid reaction have been observed after a 3- to 4-week interval.[3,23b]

22.5.3 Some Observations on Human Intoxication

Among men inadvertently exposed to HN2 vapor, 2/6 complained of nausea 3 hours after exposure and 1 vomited for 12 hours after, but these symptoms passed off by the second day. Two patients showed a polymorphonuclear leucocytosis (10,000 cells/mm³) on the first examination, but the counts fell after about 4 days to 4,000–6,000 cells/mm³, with subsequent recovery. Lymphocytes remained within normal limits, but one patient showed a temporary inversion of the polymorphonuclear leucocyte-lymphocyte ratio. An occasional "irritation" cell (Türck) was noted. Platelets tended to be on the low side of normal. Hemoglobin remained within normal limits in all cases.[101]

22.6 *tris*(β-CHLOROETHYL)AMINE (HN3, TL 145, 1070)

22.6.1 Pharmacology

Toxicity

The toxicity of HN3 is shown in Table 10. The toxicity of aqueous solutions given *ad libitum* to animals is not readily resolvable since the experiment permits aging of the solution. As judged by weight loss and food and water consumption, adult rats ingesting solutions of HN3 in tap water in concentrations of 100 and 50 ppm showed toxic reactions, while those ingesting solutions containing 25 ppm showed only minor reactions. These effects decreased as the solution aged. Adult rats intubated once with freshly prepared solutions of HN3 containing 16 ppm (0.32 mg/kg) or more, showed a progressive increase in toxic reactions with increasing concentration, and the reactions were more severe than those observed in animals ingesting presumably comparable doses during 24 hours.[23b]

When growing rats are fed solutions of HN3 in tap water, the solutions aging during the experiment, dilutions of 100, 50, and 25 ppm showed definite initial toxicity (judged by weight loss and fluid consumption) which was lost by the third day and possibly before.[36]

Pharmacodynamics

Convulsive Death. At high doses given subcutaneously in mice, intravenously in rabbits or cats, and cutaneously in rabbits, HN3 has a convulsant action. On intravenous injection in the rabbit, HN3·HCl, following a latent period, produced convulsive seizures marked by severe opisthotonus.[23b] In the cat, following a period of apprehension, the convulsions alternated between periods of opisthotonus and flexion.[36] In both species seizures recurred at lower doses, and death has been attributed to respiratory failure,

TABLE 10. Toxicity of HN3 for various species. (LD_{50} in mg/kg.)

Route / Animal	Intravenous			Subcutaneous			Cutaneous (free base)		Oral		
	LD_{50}	Remarks	Ref.	LD_{50}	Remarks	Ref.	LD_{50}	Ref.	LD_{50}	Remarks	Ref.
Mouse				2.0	HCl salt	23f, 81	7	23k			
				3.2	HCl salt	63	ca. 10	16b			
				6.9	Free base (?)	63					
				8.0-10	Free base in tributyrin	84					
Rat	0.7	HCl salt	3	2.0	HCl salt	81	4.9	23q	5	Mixed in high fat diet, 24-hr fast	56a
				2-5	Free base in tributyrin	84	2-5	84	20	Mixed in high protein diet, no fast	56a
Rabbit	2.5	HCl salt	23q	2.0	Free base	63	19	23q			
				10	Free base in tributyrin	84	5-10	84			
							15-20*	56e			
							10-20*,†	26k			
Guinea pig				7-10	Free base in tributyrin	84	20-30	84			
							10-20*,†	26k			
				2-5‡		104b					
Dog	<1.0		23q				10	56f			
Goat				20-30	Free base Neat	84	20	84			

* These values are LD_{100}'s.
† Expressed in terms of cubic millimeters instead of milligrams
‡ Report gives this value as "toxicity. . . ." Whether the free base or the hydrochloride was administered is not stated.

possibly the result of medullary anoxia. It is noteworthy that after the cutaneous application of large doses of HN3, signs of central nervous system stimulation were seen in rabbits.[26k,56e] The convulsive symptoms are less severe in subcutaneously injected mice.

The acute convulsive phenomenon can be completely prevented in cats and rabbits by the prophylactic administration of sodium pentobarbital which prolongs survival time but does not prevent death.[26c]

In the anesthetized cat no muscarinic or nicotinic responses of the blood pressure were observed. In fact, atropine does not prevent a temporary acute vasodepression in the cat following rapid intravenous injections of HN3·HCl. In doses of 5-10 mg/kg, HN3·HCl caused a gradual fall in blood pressure over a period of several hours, shock levels eventually being reached. Transitory respiratory stimulation followed intravenous injection of the compound.[26f]

Paralytic Death. Below doses which are immediately convulsive, there is a progressive development of muscular weakness, diarrhea, coldness, hyperexcitability and overactivity, retropulsive movements, tremors, and incoordination, culminating in prostration, ultimate failure of respiration, and death after a number of hours.[23e] A cat surviving a subconvulsive dose and sacrificed at 4 days manifested complete anorexia, marked paresis, moderate mydriasis and pilo-erection, and a severe leucopenia without neutropenia.[26f]

Delayed Death. With low doses, death is delayed from 3-6 days and is identical with the delayed death produced in systemic intoxication by the other β-chloroethyl vesicants.

Other Pharmacologic Properties. HN3 possesses paracympathicolytic properties. In anesthetized rabbits and cats, HN3·HCl blocked the vagal fibers to the heart,[23a,104b] and blocked the action on the heart of the parasympathomimetic drugs, acetylcholine and pilocarpine.[104b]

At a concentration of 1/150,000, HN3·HCl depressed the tonus and rhythmicity of isolated rabbit gut immersed in Tyrode's solution, and the depression was irreversible by washing. An increased tone of rabbit gut, induced by 1/60,000 pilocarpine nitrate, was depressed by HN3·HCl in a concentration of 1/30,000, and further response to the smooth muscle stimulant was prevented.[23c] Some blood changes already have been described. In rats given HN3 intravenously no alteration in blood calcium occurred.[58]

PHARMACOLOGY OF THE TRANSFORMATION PRODUCTS OF HN3

The toxicity of the transformation products and other derivatives of HN3 is shown in Table 11.

TABLE 11. Toxicity of transformation products and other derivatives of HN3. (LD_{50} in mg/kg.)
Iv = intravenous injection
Ip = intraperitoneal injection
Sc = subcutaneous injection

Substance	Remarks	Route	Animal	LD_{50}	Ref.
1,1-*bis*(β-Chloroethyl)ethylenimonium salt	A 20-minute transformation solution containing 60 per cent of the original amine as the desired product.	Iv	Rabbit	ca. 5	26i
β-Hydroxyethyl-*bis*(β-chloroethyl)amine	Hydrochloride salt dissolved in saline.	Ip	Mouse	ca. 1.5	20c
1-(β-Chloroethyl)-1-(β-hydroxyethyl)ethylenimonium salt	The chloride dissolved in saline.	Ip	Mouse	ca. 1.5	20f
	A 60-minute transformation solution containing 90 per cent of the original amine as the desired product.	Iv	Rabbit	ca. 5	26i
β-Chloroethyl-*bis*(β-hydroxyethyl)amine	Hydrochloride salt dissolved in saline.	Ip	Mouse	ca. 10	20f
		Sc	Mouse	5	77
1,1-*bis*(β-Hydroxyethyl)ethylenimonium salt	The chloride dissolved in saline.	Ip	Mouse	ca. 5	20f
	A 5½-hour transformation solution containing 80 per cent of the original amine as the desired product.	Iv	Rabbit	20-50	26i
Triethanolamine	Undiluted material.	Oral	Rat	8,000	140
			Guinea pig	8,000	140
tri-(β-Hydroxyethyl)methylammonium chloride		Ip	Mouse	ca. 100	20c
tris(β-Chloroethyl)amine oxide (HN3 amine oxide)	Saline	Ip	Mouse	ca. 3	20d

1,1-*bis*(β-Chloroethyl)ethylenimonium chloride showed no central action on intravenous administration in rabbits.[26i] There was no intense miosis or increased motor activity of the gastrointestinal tract, although there was an increase in saliva excretion. Although the animals tended to sprawl and had slight muscular weakness, the paralytic action, typical of the parent amine, was not observed. At LD_{50} doses (approximately 5 mg/kg), this derivative gave a peak leucopenia below 1,000 cells/mm³ on the third day; 2 mg/kg gave only a slight leucopenia; and with 10 mg/kg, death occurred in 36-48 hours with no leucopenia.[26i]

1-(β-Chloroethyl)-1-(β-hydroxyethyl)ethylenimonium chloride showed no central stimulatory action and only very slight parasympathomimetic action on intravenous administration in rabbits. A dose of 20 mg/kg caused a weakness of the neck and leg muscles within 30 minutes, but this action was reversible and the animals survived until 20 hours. A dose of 5 mg/kg caused a leucopenia amounting to 1,000 cells/mm³ on the fifth day, and 2 mg/kg depressed the count to 4,600 cells/mm³ on the fifth day. With 10 mg/kg early deaths precluded leucopenia.[26i]

1,1-*bis*(β-Hydroxyethyl)ethylenimonium chloride is devoid of central stimulatory and parasympathomimetic action. Within 15 minutes after a dose of 20 mg/kg a definite muscular weakness (reversible with complete recovery) appears, which may seriously impair respiration at 30 minutes. No depression of the total leucocyte count occurred at 5 mg/kg and the count was lowered to only 3,300 cells/mm³ by 20 mg/kg.[26i]

An *M*/200 aqueous solution of HN3·HCl allowed to stand at between 13 and 15 C for 2 weeks suppressed the typical cardiac vagus action possessed by the parent amine.[14b]

PREVENTION OF SYSTEMIC INTOXICATION

The systemic intoxication produced by cutaneously absorbed HN3 in the rabbit was prevented by extirpation of the HN3-contaminated skin ½ to 1 hour after the application of 15 and 20 mg/kg (LD_{50} and LD_{100}, respectively).[26c] Occasional animals were saved at either dose when extirpation was carried out at 2 and 3 hours after application. No significant success attended parenteral therapy with sodium thiosulfate[26i] — a procedure which had proved effective against intravenously administered 1-methyl-1-(β-chloroethyl)ethylenimonium chloride.[26i]

In dogs, intravenous administration of the leucocytosis-promoting factor of Menkin following the cutaneous application of 10 mg/kg (approximately LD_{50}) of HN3 free base did not alter either the speed

or magnitude of the falling total leucocyte count, and 2/3 dogs failed to survive the experiment.[23b]

BAL administered intraperitoneally in rats 6 hours after cutaneous application of a 1.5 LD_{50} dose, failed to give protection and appeared to enhance the toxicity of HN3.[23c] Medication with aminopyrine had no influence on mortality rate or survival time of mice injected subcutaneously with HN3·HCl at LD_{50} and 2 LD_{50} doses.[23a] The intraperitoneal administration of adrenal cortical extract did not consistently modify the mortality rate or survival time of rats intoxicated intravenously with an LD_{50} dose of HN3·HCl.[23r]

Special Studies on HN3 Intoxication

Occlusion of the circulation to the small intestine in dogs during and for 15 minutes following the intravenous administration of 1 mg kg of HN3·HCl partially protected the ischemic area as shown by post mortem examination.[23r] The extensive diarrhea and concomitant fluid loss were prevented, and the average survival time significantly prolonged. However, ultimate mortality was unaffected and the clinical appearance at death was essentially the same as in unoperated controls. Mild anorexia and vomiting were occasionally present and weight loss was less marked. A parallel reduction of plasma volume, extracellular fluid, and total circulating protein occurred within 24 hours but was reversed by 48 hours. A further significant reduction (less marked than in unoperated controls) occurred between 72 and 96 hours even in the absence of fluid and electrolyte loss by diarrhea. A significant leucopenia was present by 72–96 hours. In operated intoxicated dogs, daily subcutaneous saline therapy increased fluid loss by diarrhea and vomiting as compared with operated intoxicated controls not given therapy, although fluid loss was less than in unoperated controls, and did not serve otherwise to alter the clinical course of intoxication.[23r] Protection of the small intestine by occlusion of the blood supply during and for 15 minutes following the intravenous injection of HN3 did not affect the mortality rate in rats and rabbits, and only slightly prolonged survival time.[23r]

A parenteral therapy consisting of amigen, glucose, and vitamin B complex prevented significant weight loss in intoxicated dogs (1.0 mg kg intravenously) until 24 hours before death. Survival time was not prolonged, and all dogs receiving therapy died (the dose was an LD_{50}). Marked vomiting was present, although diarrhea was absent. In 2 dogs determinations 1 hour before death showed a marked reduction in plasma volume and total circulating protein. In 2 other dogs examined at the same time no significant changes were found and these 2 survived 24–48 hours after the determination.[23r]

There is no evidence of renal vasoconstriction during HN3 intoxication. After intravenous administration of 1 mg kg of HN3·HCl renal blood flow (as judged by the clearance of *p*-aminohippuric acid at low plasma levels) was increased in dogs at 24 hours or later. However, incipient upon circulatory failure, there was a terminal fall to low values, with no consistent change in the filtration fraction (glomerular filtration/renal plasma flow). The increased clearance of *p*-aminohippuric acid observed at 24 hours argues against any decrease in the extraction ratio of the substance and thus against specific renal tubular injury.[23i]

In 4 dogs receiving daily intravenous injections of 0.1 mg kg of HN3·HCl, the clinical symptoms characteristic of higher doses were absent, and the only evidence of intoxication was a moderate reduction in the total leucocyte count. In each instance, recovery of the count began before the tenth day.[23r]

In rats intoxicated intravenously with 1.0 mg/kg of HN3·HCl, there appears to be increased capillary permeability of the intestinal wall. The injection of Evans blue dye (T-1824) at 48 and 96 hours after intoxication was followed by appearance of the dye within 3 minutes in the intestinal wall of intoxicated rats with ligated bile ducts. At this time the fluid and watery intestinal contents showed increasing coloration, whereas there was no significant coloration earlier (8 and 24 hours) when the intestinal contents were still solid.[23i]

However, the disappearance rate of T-1824 in dogs intoxicated by 1 mg kg of HN3·HCl intravenously administered revealed no significant increase by the third day of intoxication as compared with the same animals before intoxication. Thus, any possible increase in the permeability of the capillaries to albumin in the dog was less than the errors of the dye method. The possibly significant increase in the disappearance rate observed after the infusion of fluids on the third day of intoxication would tend to indicate an increased loss of albumin which agreed with the deficit of the total circulating protein (balance studies) in these dogs within an hour after fluid infusion.[23r]

Studies in water and electrolyte balance in dogs, following the cutaneous application of 20 mg kg, have shown that an increased fluid intake paralleled

by an increased fluid output began within 24 hours and persisted through the survival. Accompanying the exaggerated rate of water exchange was a marked loss of extracellular and intracellular electrolytes. The loss of extracellular electrolytes, attributable only in part to vomiting, resulted chiefly from a renal defect in the tubular reabsorption of sodium and chloride. Approximately 50 per cent of the intracellular electrolyte (potassium) was accounted for by increased catabolism, presumably of the lymphoid tissue. The loss of the additional increment of potassium is unexplained. In some animals, extracellular fluid volume was maintained at the expense of osmotic dilution; in others, osmotic homeostasis was maintained at the expense of extracellular fluid volume. Still other animals showed an intermediate course. Variations in the hematocrit and in serum protein concentration were related to variations in extracellular fluid volume and concentrations of extracellular sodium. The wastage of extracellular electrolytes exhibited by the HN3-poisoned dogs was not unlike that encountered in adrenal insufficiency, although serum potassium did not rise and no pathologic change was evident in the adrenals.[45]

22.6.2 Systemic Pathology of HN3 Intoxication

In producing systemic pathology in rats, HN3 ranks second to HN2 when all routes of administration are considered and the systemic injury is judged by lymphoid atrophy, myeloid injury, leucopenia, enteritis, and weight loss. The wide variation in total systemic injury from route to route in H intoxication is not seen with HN3, although, as is the case with all the agents, variations in the severity of a single lesion are observed from route to route. Table 12 shows the intensity of total systemic injury and of individual lesions in the rat following the administration of LD_{50} doses by various routes.

At sub-LD_{50} levels these lesions maintain approximately the same relationship to one another, with the exception of leucopenia, but they are reduced in intensity. Moderate to severe leucopenia was observed in all cases, except after gassing, following which leucopenia was mild. Severe diarrhea was noted after cutaneous application, slight diarrhea after intravenous injection, and none was noted after gassing.[14,23b,n,o,q]

In rabbits systemic injury is slightly less than in rats following intravenous administration and is about the same in both species following cutaneous administration. Intravenous administration caused moderate myeloid injury and mild lymphatic atrophy, which were together reflected in a moderate leucopenia. Weight loss was moderate, and the enteritic lesion was mild.[23n] Applied cutaneously, HN3 caused moderate lymphatic injury, mild myeloid injury, moderate leucopenia, moderate weight loss, and mild enteritis. The hematologic changes consisted of lymphopenia accompanied by a granulocytosis on the first day. The lymphocytes remained reduced in number during 4 days. On the third day a granulocytopenia became apparent. Toxic polymorphonuclear leucocytes were observed on the third and fourth days.[23]

In mice given HN3·HCl subcutaneously, a reduction of circulating lymphocytes coincidental to severe injury to the lymphoid tissue, culminated within 24 hours. Immature granulocytes disappeared in 24–48 hours and mature polymorphonuclear leucocytes decreased markedly in number on the third or fourth day, paralleling the later-appearing damage to the bone marrow. The only other changes were edema and superficial erosions in the tips of the intestinal villi and regenerative activity in the crypts with no consistent intramural changes.[23r]

In mice receiving 0.05 mg kg of HN3·HCl daily for 10 days by subcutaneous injection, mild leucopenia

TABLE 12. Systemic effects in rats of LD_{50} doses of HN3.

These data are an average of data reported in detail.[14] The abbreviations iv, sc, cut, and gas represent respectively intravenous, subcutaneous, and cutaneous application, and exposure of the whole body to the agent dispersed by atomization. Intravenously and subcutaneously, a solution of HN3·HCl in physiological saline was administered. The free base was applied to the skin.

Route	Lesion: Total systemic injury	Lymphoid atrophy	Myeloid injury	Leucopenia	Enteritis	Weight loss
Iv	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Sc	Moderate	Moderate	Mild	Absent	Moderate	Moderate
Cut	Moderate	Moderate	Mild	Moderate	Severe	Mild
Gas	Moderate	Mild	Moderate	Severe	Moderate	Moderate

appeared on the fourth day and lowered counts were prevalent during the remainder of, and for 5 days after, the injection period. A moderate to severe reduction of the absolute number of lymphocytes characterized the entire injection period and recovery phase. The polymorphonuclear leucocyte counts were more variable and indicated a variable leucocytosis. Reduction of the erythrocyte count and of the hemoglobin level were observed, but these changes occurred later than the changes in the white cell count. Thrombocytes were not at any time reduced and were occasionally increased.[58]

Histologic examination of the myeloid tissue indicated that normoblastic changes were confined primarily to the polychromatophilic stage. Myeloblasts were not involved apparently, but a striking increase in polymorphonuclear promyelocytes occurred. Myelocytes showed no significant change, but a two- to threefold elevation occurred in the percentage of metamyelocytes. Megakaryocytes were generally increased.[58]

During recovery, polychromatophilic normoblasts rapidly returned to normal or supranormal levels, while the promyelocytes and metamyelocytes rapidly fell to normal levels.[58]

It has been concluded that small intravenous doses of HN3 repeated daily in the rabbit have, after an intermediate slight depression, a stimulatory effect on heterophilic polymorphonuclear leucocytes, and a mildly depressive effect on lymphocytes. In view of the complexity of the procedures, the original report should be consulted for details.[57]

Leucopenia has been described for mice exposed for 10 minutes to 0.75 mg l of HN3,[5] in rats ingesting solutions containing 100 and 50 ppm, and in rats intubated with a single dose.[ ]

Characteristic pathologic changes have been reported after subcutaneous and cutaneous administration in other species as well as in the above animals. In addition, cardiac dilatation with flabbiness of the right side, and congestion of the liver, spleen, adrenals, and kidneys were reported.[6]

The usual systemic injury was observed in dogs receiving 10–40 mg/kg of HN3 on the clipped shaved skin. In addition renal necrosis involving the epithelium, mainly of the distal convoluted tubules, was considered a significant lesion relative to the marked changes in electrolyte excretion which occur in HN3 intoxication.[58] Renal necrosis has not been reported elsewhere and lacks confirmation in other species and other routes of administration.

22.6.3 Some Observations on Human Intoxication

Six subjects in terminal stages of incurable diseases were given repeated daily intravenous doses of 0.1 mg/kg of HN3·HCl in a course consisting of 3–10 injections. Nausea, vomiting, headache, malaise, and drowsiness were the only immediate untoward systemic effects observed. Local reactions consisted of thrombophlebitis, and slough at the site of extravasation. The hematopoietic response consisted of absolute lymphopenia, progressive normochromic anemia, thrombocytopenia, and severe leucopenia, with granulocytopenia. During the developmental phase and again during the recovery phase a striking shift to the left occurred in the Schilling differential. Symptomatic therapy with blood transfusions and pentnucleotide seemed at times favorably to affect the clinical course and to initiate the recovery phase.[58]

In normal volunteers, the intravenous administration of a single dose of 0.1 mg/kg of HN3·HCl induced headache appearing within 9 hours and persisting for periods as long as 11 hours, and nausea appearing within 9 hours and persisting from 1–3 days. Vomiting and anorexia did not occur. Dizziness and weakness were felt by 2–4 subjects. All 4 subjects developed thrombophlebitis.

Blood studies showed decreases of lymphocytes from an average control value of 2,500 cells/mm³ to 700 cells/mm³ between the third and sixth days. The counts returned to normal by the fourteenth to twentieth days. Fasting blood sugar levels and electrocardiograms showed no changes in 2–2 subjects.[58] A thrombocytopenia has been observed after intravenous intoxication.[61]

In volunteers ingesting 2–6 mg of HN3·HCl freshly dissolved in tap water, symptoms consisted of anorexia, recurrent nausea and vomiting, tenseness and fullness in the epigastric region, gaseous eructations, and occasional mild diarrhea. Lassitude and mild depression were also prominent. These symptoms were more pronounced following doses of 4 and 6 mg, were mild at 2 mg, and were absent or slight at 1 mg. Recovery was complete in 48 hours.[55a]

The oral ingestion of 1 mg 3 times daily for 5 days was tolerated with moderate symptoms; recovery promptly occurred on withdrawal of the agent. In those subjects ingesting a total of 15–18 mg, a moderate leucopenia became apparent in 5–7 "within 7–9 days after the start of the drinking, and was more or less persistent in all instances for periods beginning

7–25 days after the first doses and continuing for as long as 7 weeks after the first dose." Similar but less pronounced or definite changes were observed in men consuming a total of 7–9 mg and no significant changes were seen in those ingesting 3–5 mg. Among the subjects ingesting single doses, only one (6 mg) developed a transient leucopenia 10 days later. In all cases there was no significant alteration of erythrocytes.[18] A recheck of these subjects 18 months after the experiment showed no further disturbances specifically referable to the agent.[36a]

Among subjects ingesting varying doses (based on the parent amine) of solutions of HN3, hydrolyzed so that 1,1-*bis*(β-hydroxyethyl)ethylenimonium chloride predominated, only those (2/2) ingesting the highest dose (24 mg) showed symptoms, consisting chiefly of nausea and vomiting. There were no changes in any subject in hemoglobin level, white blood cell count, hematocrit, or differential smears during 30–36 days after ingestion.[36c]

In addition to local irritation (eyes and upper respiratory tract), headache and vomiting have been noted among humans inadvertently exposed to HN3 vapor. During hospitalization no changes in body temperature, pulse rate, or blood pressure were observed and urine analyses were normal.[18a]

22.7 ISOPROPYL-*bis*(β-CHLOROETHYL)-AMINE (ISOPROPYL-S, TL 301)

The LD_{50}'s of TL 301 administered as its hydrochloride to various species by various routes are given in Table 13. TL 301 is more toxic than HN2

TABLE 13. Toxicity of isopropyl-*bis*(β-chloroethyl)amine for various species. (LD_{50} in mg/kg)

Route	Animal	LD_{50}	Reference
Sc	Mouse	1.1	16, 23c, 81
		ca. 0.5	
	Rat	1.0	23b, 81
		ca. 2.0	
Iv	Rat	0.5	23c
	Rabbit	ca. 2.0	23c
Oral	Mouse	22.0	23c

or HN3 when injected into animals in an aqueous solution of its hydrochloride. After subcutaneous administration in the mouse, the LD_{50} of an aqueous solution allowed to stand until equilibrium is obtained is between 10 and 20 mg/kg. This solution has only one-tenth the neurotoxic action of similar hydrolysates of HN2.[23]

TL 301 possesses parasympathicolytic action, slowly blocking vagal inhibition of the heart in the anesthetized rabbit in doses of 20 to 30 mg/kg given intravenously. Unlike the action of atropine, which is readily reversible, the action of this amine and its analogs is irreversible. Unlike HN2, TL 301 does not stimulate the isolated intestine at low concentrations. Higher concentrations, however, produce marked depression, which is overcome by immediate washing but not by pilocarpine. Its parasympathomimetic action is less marked than that of HN2 and such phenomena as have been observed with TL 301 may be central in origin.[3,23b,c] Parenteral administration of LD_{50} doses results in blood changes similar to those produced by other β-chloroethyl vesicants, namely atrophy of lymphoid tissue and aplasia of the bone marrow.[3,23b,c,57a] Gassing mice with a vapor dosage equivalent to three times the $L(Ct)_{50}$ results in essentially the same hematologic and pathologic changes.[5,16] It has been concluded that small intravenous doses of TL 301 repeated daily in the rabbit have, after an intermediate slight depression, a stimulatory effect on heterophilic polymorphonuclear leucocytes, and a mildly depressive effect on lymphocytes. In view of the complexity of the procedures, the original report should be consulted for details.[57d]

1-Isopropyl-1-(β-chloroethyl)ethylenimonium chloride also has a leucotoxic action.[23i]

22.8 COMPOUNDS RELATED TO NITROGEN MUSTARDS

In Table 14 some of the compounds related to the nitrogen mustards are tabulated.

It has been emphasized that all leucotoxic compounds in Table 14 are capable of cyclizing to form imonium ions.[23i] Extending this comparison, a correlation has been observed between the subcutaneous toxicities of the hydrochlorides of various amines and the half-life times of the amines in aqueous solution at 37° C and *p*H 7.4 (Table 15).[13] It appears that the toxicity varies inversely as the half-life, or directly as the lability of the amine, when allowance is made for the scatter usually encountered in toxicity determinations. This circumstance is not inconsistent with the deduction from chemical data that physiological reaction of the nitrogen mustards proceeds through the intermediation of the cyclic imonium ion.

It is possible that correlation of toxicity with reactivity extends beyond lability of the amine and perhaps includes reactivity of the cyclic imonium

TABLE 14. Toxicity of compounds related to nitrogen mustards.

A compound with an LD_{50} by subcutaneous injection <25 mg/kg is arbitrarily considered toxic; >25 mg/kg, nontoxic. Unless otherwise specified in footnotes, the compound was administered as the hydrochloride.

N.T. = nontoxic by screening study
T. = toxic by either screening (scr) study, or definitive (def) study

Compound examined	Remarks	Ref.
I. *Compounds containing one β-chloroalkyl group per N atom*		
A. Secondary amines		
1. Methyl-β-chloroethylamine	N.T., neurotoxic, nonleucotoxic	23g
2. Ethyl-β-chloroethylamine	N.T., neurotoxic, nonleucotoxic	23g
B. Tertiary amines		
1. Diethyl-β-chloroethylamine	N.T.	16i, 23e, 26i
	Neurotoxic	23g
	Nonleucotoxic	23g, 26i
2. Dimethyl-β-chloropropylamine	N.T.	16i
C. Quaternary salts		
1. Trimethyl-β-(chloroethylthio)ethylammonium chloride*	T. (def)	1
II. *Compounds containing two β-chloroalkyl groups per N atom*		
A. Secondary amines		
1. *bis*(β-Chloroethyl)amine	N.T.	23f, 104b
	Leucotoxic at LD_{50}	23f
B. Tertiary amines		
1. Allyl-*bis*(β-chloroethyl)amine	T. (def)	16j, 23f, 63
	Leucotoxic at LD_{50}	23f
2. Propyl-*bis*(β-chloroethyl)amine	T. (def)	16i, 81
	Leucotoxic	57a
3. Butyl-*bis*(β-chloroethyl)amine	T. (scr)	16i
4. *sec*-Butyl-*bis*(β-chloroethyl)amine	T. (scr)	16i
5. *tert*-Butyl-*bis*(β-chloroethyl)amine	T. (scr)	16i
6. *iso*-Butyl-*bis*(β-chloroethyl)amine	T. (scr)	16i
7. *bis*(β-Chloroethyl)-β-chloroallylamine	Leucotoxic	57c
8. *bis*(β-Chloroethyl)-β-propynylamine	Leucotoxic	57c
9. *bis*(β-Chloroethyl)-β-methoxyethylamine	T. (scr)	16i
10. Cyclohexyl-*bis*(β-chloroethyl)amine	T. (scr)	16i
11. Benzyl-*bis*(β-chloroethyl)amine	N.T. (scr)††	16i
	Leucotoxic	57a
12. Furfuryl-*bis*(β-chloroethyl)amine	T. (scr)	16l
	Leucotoxic	57b
13. *bis*[β-[*bis*(β-Chloroethyl)amino]ethyl] sulfide	T. (scr)	16l
14. Vinyl β-[*bis*(β-chloroethyl)amino]ethyl sulfone	T. (def)	20m, 23w
15. N,N,N',N'-*tetrakis*(β-Chloroethyl)ethylenediamine	T.	16j, 23p
	Neurotoxic,† leucotoxic	23p
16. *bis*(β-Chloroethyl)-γ-chlorobutylamine	T. (scr)	16k
	Leucotoxic	57a
17. Methyl-*bis*(β-chloroethylthioethyl)amine	T.	16j
	Leucotoxic	57c
18. Ethyl-*bis*(β-chloroethylthio)ethylamine	Leucotoxic	57c
19. Methyl-*bis*(β-chloropropyl)amine	Neurotoxic,‡ leucotoxic	23g
C. Quaternary salts		
1. *bis*(β-Chloroethyl)dimethylammonium chloride	N.T.	16h, 23f
	Nonleucotoxic	23f
2. Ethyl-vinyl-*bis*(β-chloroethyl)ammonium chloride	N.T.	16o
3. *bis*(β-Chloroethyl)morpholinium chloride	N.T., nonleucotoxic	23f

* Classification arbitrary.

† Severe neurologic disturbances greater than those seen with the nitrogen mustards, often followed by rapid death. Death may occur 18 hours after injection and is attended by severe pulmonary injury. Systemic effects are qualitatively similar to those produced by nitrogen mustards.

‡ Impure; compound in saline.

§ In propylene glycol.

¶ In propylene glycol or neat.

Free base as well as the hydrochloride.

** Nontoxic as the free base.

†† Neat.

SECRET

TABLE 14. (*Continued*)

Compound examined	Remarks	Ref.
D. Unclassified		
1. *bis*(β-Chloroethyl)chloroamine	N.T.,‡ Neurotoxic, nonleucotoxic	23z
2. *bis*(β-Chloroethyl)nitrosoamine	N.T.§	23f,g
	Neurotoxic	23g
	Nonleucotoxic	23f
3. N-*bis*(β-Chloroethyl)formamide	N.T.,‖ Neurotoxic, nonleucotoxic	23g
III. *Compounds containing three β-chloroalkyl groups per N atom*		
1. *bis*(β-Chloroethyl)-β-chloropropylamine	T. (def)[¶]	63
2. β-Chloroethyl-*bis*(β-chloropropyl)amine	T. (def)[¶]	63
IV. *Compounds containing four β-chloroalkyl groups per N atom*		
1. *tetrakis*(β-Chloroethyl)ammonium chloride	N.T.	20c
V. *Unclassified*		
1. Diethyl-δ-chloropentylamine	N.T.	16m

TABLE 15. *Comparison of reactivity and toxicity of amines.*

I.D.$_{50}$'s are expressed in mg/kg for mice by subcutaneous injection of the hydrochloride dissolved in saline. The term $t_{\frac{1}{2}}$ (in minutes) measures the time necessary for one-half of the amine to cyclize to the ethyleniminonium ion under physiological conditions (*p*H 7.4, 37 °). The term k_w is the second-order specific reaction rate for the reaction of the ethyleniminonium ion with water.

Compound	*I.D.*$_{50}$	Amine reactivity $t_{\frac{1}{2}}$	Ethyleniminonium reactivity k_w
Isopropyl-*bis*(β-chloroethyl)-amine	1.1	0.094	1.30
Ethyl-*bis*(β-chloroethyl)amine	1.2	0.26	0.67
Propyl-*bis*(β-chloroethyl)amine	1.9	0.160	0.95
Butyl-*bis*(β-chloroethyl)amine	ca. 2.0	0.24	
tris(β-Chloroethyl)amine	2.0	0.44	31.0
Methyl-*bis*(β-chloroethyl)amine	2.6	1.5	0.90
bis(β-Chloroethyl)-β-methoxy-ethylamine	ca. 3.0	0.64	
Methyl-β-chloroethyl-β-hydroxy-ethylamine	16.0	3.3	0.23
Diethyl-β-chloroethylamine	<100	2.7	~0.01
Ethyl-β-chloroethylamine	1,000	825	
Methyl-β-chloroethylamine	>1,000	965	

ion.[13] According to this hypothesis, the amine yielding the most reactive imonium ion should manifest the highest toxicity. Column 4 in Table 15 shows the reactivity of the ethyleniminonium ions of some of the amines in column 2. Comparison of columns 2 and 4 shows that changes in order (e.g., HN1 and HN3) are more serious and possibly equivocate the correlation between toxicity of the amine and reactivity of the imonium ion. However, it may be emphasized that the reaction rates in column 3 are determined in homogeneous solution and may not be applicable to complex biological systems. Thus, the low toxicity position of HN3 compared to the high reaction rate of the 1,1-*bis*(β-chloroethyl)ethyleniminonium ion, may be accounted for by too rapid hydrolysis of the ring, or an even faster reaction with some non-essential cellular constituent, as compared with its reaction rate with some essential cellular constituent.

Paucity of data prohibits the comparison of the toxicity of the ethyleniminonium ions with their reaction rates. The pertinence of such a comparison is, moreover, doubtful, since the amine probably enters the cell with greater facility than the imonium ion.

Chapter 23

MECHANISMS IN PRODUCTION OF CUTANEOUS INJURIES BY SULFUR AND NITROGEN MUSTARDS*

By *Birdsey Renshaw*

23.1 INTRODUCTION

THIS CHAPTER is concerned with basic mechanisms involved in the production and mitigation of cutaneous injuries produced by vesicants of the sulfur and nitrogen mustard series. Attention will be focused principally upon laboratory studies. The data and concepts concerning practical problems relating to the skin injuries produced by these agents in the field have recently been summarized elsewhere.[28]

It is considered that one purpose of this review is to provide future investigators in the field of skin physiology and toxicology with a guide to the information and ideas gained in the course of chemical warfare investigations during World War II. Attention is therefore given not only to the results of studies that have culminated in definitive results of practical importance, but also to various observations of an incomplete but provocative character.

The majority of the investigations have entailed the use of mustard gas [*bis*(β-chloroethyl) sulfide], H. Among the other agents that have received attention are "one-armed" mustards such as benzyl β-chloroethyl sulfide (benzyl-H); sesquimustard, 1,2-*bis*(β-chloroethylthio)ethane (Q); *bis*(β-chloroethylthioethyl) ether (T); and the nitrogen mustards, ethyl-*bis*(β-chloroethyl)amine (HN1), methyl-*bis*-(β-chloroethyl)amine (HN2), and *tris*(β-chloroethyl)-amine (HN3).

Some of the principal findings may be summarized as follows. When H is applied to human skin as liquid or as saturated vapor, it penetrates at a rate of about 1 4 μg cm^2 min at an environmental temperature of 75 F. About 12 per cent of the penetrating molecules rapidly react with and are "fixed" by nondiffusable components (principally proteins) of the skin. The remaining 88 per cent are carried away by the circulation. Considerable indirect evidence suggests that the fixation of H molecules by skin proteins is the initial step in the chain that culminates in gross cutaneous injury. The intermediate steps have not adequately been elucidated. Lesions of vesicating severity are associated with the penetration of only 5–20 and the fixation of only 1 or 2 μg of H per square centimeter of skin (i.e., with exposures of only a few minutes' duration at 75 F and of even shorter times at higher temperatures). Even when human skin is massively contaminated with liquid H there is never within the skin any significant quantity of free H that is not removed by surface decontamination, i.e., by surface application of chlorinating agents or by liberal washing with H solvents. Therefore, therapeutic attempts based on destruction of free penetrated H must be essentially valueless. Moreover, no significant success has been achieved in attempts to remove fixed H from the skin by procedures which do not themselves produce severe injury, or in other attempts at early or late treatment of H injuries. Thus, at the present time the practical means of combating the skin-injurant action of H are to prevent the agent from reaching the skin and, once it has reached the skin, to effect surface decontamination as rapidly and completely as possible.

So far as is known, the other sulfur and nitrogen mustards behave much as does H except for quantitative differences in penetration rate and in injury-producing effectiveness of the penetrating molecules.

23.2 GROSS AND MICROSCOPIC PATHOLOGY OF VESICANT BURNS

23.2.1 Pathology of Vesicant Burns on Human Skin

General Macroscopic and Clinical Observations

Depending upon the severity of exposure and the susceptibility of the exposed tissue, a vesicant may produce cutaneous injury characterized at its peak by macroscopic changes varying from faint and transient erythema to coagulation and necrosis of the entire epidermis and dermis (corium). The manifestations of injuries progressively more severe than threshold are: erythema (E) of increasing intensity, raised (edematous) erythema (E'), scattered small

* Based on information available to the National Defense Research Committee, Division 9, as of March 1, 1946.

"pinhead" vesicles (PHV), and one or several large blisters or vesicles (V). In the case of still more severe burns the central region may be so severely injured that the processes leading to the accumulation of edema fluid are arrested before a blister is produced. The lesion is then characterized by a flat region of coagulated epidermis and corium, often surrounded by a narrow annular ("doughnut") vesicle. Occasionally small, relatively mild lesions on the skin of the forearm develop necrosis, characterized by a whitish centrum on an area of erythema, without or previous to the formation of macroscopically visible vesicles.[32] Furthermore, men exposed to the vapors of H or nitrogen mustards in field and chamber trials, particularly under hot and humid conditions, frequently develop on various parts of the body areas of dry and or moist maceration and desquamation without the intermediation of vesicle formation.[31,32,127] The skin of the scrotum and penis frequently reacts in this way, although upon occasion large blisters may develop upon the genitals as well as upon other so-called sensitive areas (e.g., the axillae).[31,104,127]

The degree of incapacitation produced by a vesicant burn depends upon its location and size as well as upon its severity. Other things being equal, various types of lesions may be grouped in ascending order of incapacitating potency as follows:[127,129]

1. Faint erythema.
2. Definite erythema, equivalent to faint erythema with dry desquamation.
3. Definite erythema with dry desquamation or pinhead vesication, equivalent to raised (edematous) erythema.
4. Definite erythema with areas of moist desquamation or frank vesication, equivalent to raised (edematous) erythema with dry desquamation or pinhead vesication.
5. Raised erythema with areas of raw desquamation or frank vesication.

Regardless of the ultimate severity that an H lesion may attain, there is an initial post-exposure period, usually of one to several hours' duration, during which there is neither clinical nor macroscopic evidence that injury has been sustained.[32,51,56] Erythema then develops, to be followed by the further changes if the injury is sufficiently severe. Inasmuch as the interval between exposure and the initiation of irreversible biochemical changes is very brief (see Sections 23.3.2 and 23.4), the major part of the nonreactive period is to be regarded as an interval between injury and grossly visible reaction rather than as an interval between exposure and injury. Negative though macroscopic evidence is, however, careful cytological observations and physiological studies on the blood vessels of the dermis do reveal that detectable pathological changes have set in within a few minutes after application of liquid H to human or animal skin (see Sections 23.2.4 and 23.2.5).

In the case of circumscribed experimental burns on the skin of the forearm or abdomen, the height of the reaction frequently is not attained within 24 hours but *usually* is reached within 48 hours.[32,59] The appearance between 24 and 48 hours thus suffices to give a good measure of the extent and nature of the damage that has been sustained.

Representative data on the time course of the development and healing of circumscribed experimental H and nitrogen mustard (HN3) burns of moderate severity on forearm skin are presented in Table 1. On the other hand, injuries caused by small doses of liquid H and 2-chloro-1,3-*bis*(2-chloroethylmercapto)propane sometimes take about a week to attain maximum severity as evidenced by macroscopic appearance.[56] The results of field and chamber

TABLE 1. Development and healing of injuries produced by the vapors of H and HN3 on skin of the human forearm.[59]

Edgewood-type vapor cups were applied to the skin of the forearms of six men at a room temperature of 80 ± 1 F and relative humidity of 51 per cent. The exposure time to H was 10 minutes; to HN3, 100 minutes. Inasmuch as the volatility of H is about eight times that of HN3, the vapor dosages (*Ct*'s) were *approximately* equal (i.e., H = 0.8 × HN3).

Appearance of skin	H	HN3
First trace of erythema (E-?)	1 ± hours	1 − hours
Definite erythema (E)	2-3 hours	1.5-2.5 hours
Raised (edematous) erythema (E+)	8-12 hours	4-8.5 hours
Pinhead vesication (PHV)	13-22 hours	(13) hours*
Coalesced blister (V)	16-48 hours	(16-18) hours*
Maximum-sized blister or necrotic area*	48-72 hours†	54-72 hours*‡
Complete denudation of skin surface	6-9 days	8-12.5 days
Removal of scab	20-28 days	16-25 days
Complete healing	22-29 days§	17-36 days

* Four of the six HN3 lesions progressed from the E+ stage to a pinhead necrotic lesion without the formation of vesicles. The difference with respect to the H lesions in this sense is to be regarded as dependent at least in part upon chance and upon the dosage employed and not necessarily upon a characteristic difference between the effects of H and HN3. It can also produce necrosis without vesicle formation.

† Average = 52 hours.

‡ Average = 54 hours.

§ Average = 25+ days.

Average = 23+ days.

trials also indicate that the development of injury, and certainly the maximum incapacitation that results from it, are considerably delayed after exposure to mild and moderate dosages of H vapor (i.e., dosages sufficient to produce "injury without disability" or "partial disability," but not "total disability."[48] Fresh vesicles sometimes appear on various parts of the body as late as 7–12 days after exposure.[70,124,140] Analysis of the results of an extensive series of trials in the tropics reveals that more men were incapacitated at 10–12 days than at earlier or later times after exposure.[137] In spite of this delay, however, it is said to be possible as early as the first day to make a fairly satisfactory prognosis of the degree of incapacitation that will later develop.[140] The apparent difference between the times for maximum development of circumscribed experimental burns and of the more extensive burns sustained on various parts of the body in field and chamber trials may be due, in part, to differences in the severity of the two types of burns as usually studied and in the criteria used in evaluating them. It may also be due in part to other factors, such as the size and location of the injured areas of skin (see Section 23.7). The results of field and man-chamber trials show that in the case of very severe vapor burns, and also of liquid burns which are almost always severe, macroscopic injury develops rapidly and maximum incapacitation is sustained within 1–2 days.[48]

A number of observations have been made on the healing time of vesicant burns.[12,43,79,85,118,127] Again, both size and severity, and possibly the post-exposure conditions as well, are important factors. When the injury is sufficient to destroy the entire epidermis and much or all of the corium (i.e., necrotizing lesions), the healing of even small areas is slow (i.e., 6–8 weeks). Dosages insufficient to destroy the corium and the deeper islands of epithelial cells may still produce vesication, but the healing time as evidenced by epithelialization may then be considerably shorter (i.e., 2–4 weeks).

Preliminary observations have been made on the electrical correlates of developing and healing chemical burns.[46]

Histological Study of Biopsied H Burns

The National Defense Research Committee [NDRC] group at Harvard University has made a histological study of a large series of experimental H burns of varying severity.[12,13] Liquid H was applied to circumscribed areas of human abdominal skin and the sites were decontaminated after predetermined exposure times. Sixty-one exposed sites were examined histologically after surgical excision at intervals up to 38 days after exposure. The severity of the injury was determined principally by the exposure time and the environmental temperature. Three *broad* categories of injury were defined and may be described as follows:[b]

1. *Mild or subvesicating injuries.* The lesion reaches its acme with little or no vesication (i.e., at most a few miliary blisters develop). Microscopic examination of sites excised 3–6 hours after exposure show swelling of nuclei throughout the malpighian layer of the epidermis, and hyperemia and edema of the tips of the dermal papillae. The central portions of the affected nuclei become homogeneously pale and the remaining chromatin is scanty in amount and peripheral in position. The nuclear swelling does not necessarily indicate that irreversible damage has been sustained, for many of the cells recover. Twelve to eighteen hours after exposure, however, the swollen nuclei of some of the cells become pyknotic, and lysis and disintegration of their cytoplasm takes place. This liquefaction necrosis usually is undergone by small groups of cells located in the deepest portion of the malpighian layer immediately above the tips of the dermal papillae. There is no through-and-through destruction of the epidermis if the injury remains mild; the foci of necrosis do not continue to enlarge and so remain macroscopically invisible, or at most lead to the formation of miliary blisters. In the mildest injuries the irreversible damage (necrosis) involves individual cells rather than groups of cells.

The injury often reaches its peak so far as the epidermis is concerned within 24–48 hours, but occasionally 4 days elapse before the full extent of irreversible change is apparent. The injury is then characterized by: (a) diffuse nuclear swelling throughout the malpighian layer, with varying degrees of loss of chromatin; (b) pyknosis of nuclei within some cells that otherwise appear to be intact; (c) foci of liquefaction necrosis in the deepest layer of the epidermis immediately above the dermal papillae; and (d) hyperemia, edema, and perivascular mononuclear infiltration of the dermal papillae.

At 3–4 days after exposure the mild injury is characterized by (a) augmented desquamation, lead-

[b] The results are in general accord with those based on a smaller series of burns of the forearm and presented in a report [43] in which the earlier literature is reviewed.

ing to the disposal of dead cells; and (b) augmented mitotic activity in the basal layer, leading to the replacement of the destroyed cells. These processes may be observed for as long as a week after exposure. In some individuals there is an accretion of pigment around the lesion and a persistent state of irritation of the vessels of the underlying dermis.

2. *Vesicating injuries.* During the first 6–12 hours of the reactive period the microscopic changes are similar to those seen in cases of mild injury. However, the microscopic foci of liquefaction necrosis present at the end of 12 hours continue to enlarge and coalesce, so that eventually all or most of the exposed epidermis becomes separated from and elevated above the dermis. As the blister develops with the further accumulation of fluid, erythema gives way to ischemia and the lesion becomes pale. The blister fluid consists to a small extent of the detritus of broken-down cells and to a large extent of edema fluid. Although most of the disruption of epidermis from dermis occurs at the site of liquefaction necrosis, there is evidence that the traction exerted on living and relatively undamaged cells at the margins of vesicles frequently enlarges the lesions beyond the limits of the original cytotoxic damage. There is more pronounced exudation of mononuclear and polymorphonuclear cells in the dermis than occurs in mild lesions, and subsequently there is desiccation and coagulation necrosis of all or most of the corium. Beginning ingrowth of epithelium from the normal epidermis at the margin can usually be recognized within 72 hours after exposure.

Despite this early evidence of regenerative activity, the damaged corium is at first incapable of maintaining the newly regenerated epidermis. Not until about the second week is the marginal ingrowth of epithelium able to survive, and not until between 4 and 5 weeks after exposure is the epidermal defect completely and permanently healed. The slowness with which permanent epithelialization is accomplished apparently depends on the functional state of the dermis. In the beginning new epithelium grows over a dermis that is dead or dying. Frequently a brightly acidophilic zone of necrotic collagen can be recognized between viable dermis and new epidermis. Later the tentative epidermis is supported by a dense cicatrix. Finally, the last and successful crop of regenerated epithelial cells is supported by a vascularized layer of loose connective tissue that bears a close resemblance to the original corium.

3. *Coagulation necrosis.* The most severe type of injury leads to the formation of a lesion that shows vesication only at its outermost margin ("doughnut" or annular blister). Throughout the center of the lesion the skin is tanned or coagulated in such a manner that fluid never accumulates in sufficient amounts to separate the dead from the living cells. Macroscopically the centrum becomes pale and takes on an opaque, parchment-like appearance. In the early stages of reaction such an injury is microscopically indistinguishable from milder lesions. In some instances abortive foci of liquefaction necrosis appear, and in other instances nuclear swelling and pyknosis occur throughout the entire thickness of the epidermis. However, other immediate morphological changes in cells or in intercellular relationships do not develop.

The necrotic epidermis retains all or a large part of its connection with the dermis, and a week or more elapses before a zone of demarcation between the dead and the living tissue becomes recognizable. The epidermis together with the adjacent zone of necrotic dermis remains *in situ* and desiccates to form a plate-like sequestrum which apparently interferes with healing so long as it remains interposed between the margins of the defect.

Whereas the final epithelialization of a vesicating type of injury is usually accomplished within 4–5 weeks, this more severe type of lesion may require several weeks longer to heal.

23.2.2 Pathological Changes in Animal Skin

General Observations

The effects of vesicants on animal skin have been extensively studied and are of importance because of the frequent unavailability of human material for experiments on the mechanism of vesicant action, decontamination, and treatment. More or less complete descriptions of the sequence of pathological changes due to applications of H have been reported for the pig,[12,24] goat,[55] dog,[55] rabbit,[12,20,27,54] cat,[46,112] and mouse.[63,106,131]

There are several obvious anatomical differences between human and animal skin. The skin of most suitable test animals contains no sweat glands in the regions where extensive tests can practically be carried out (i.e. the glands are limited to the toe pads and snout), and it possesses fewer layers of epithelial cells but many more hair follicles than the skin of man. These differences may affect the rate and mode of penetration of vesicants and of possible therapeutic agents as well.[21]

The most conspicuous difference between the pathological responses of human and animal skin to agents such as H and the nitrogen mustards is that animal skin usually does not vesicate. Exceptions to this generalization are described below. As an explanation of the absence of vesicle formation it has been suggested that animal skin, because of its thin epidermis, is so completely coagulated that extensive accumulation of fluid is impossible. The inadequacy of this interpretation is made evident by the finding that vapor dosages, ranging from those which suffice to produce only threshold injury to those which destroy the entire skin, ordinarily do not produce vesicles on the usually tested areas of the body surface of pigs and other animals.[12] It has not been determined whether the absence of vesication in animals is due to the elicitation of a different kind of exudative response or to a firmer and less destructible anchorage between the epidermis and the corium.

Another gross difference is that injuries on animal skin usually develop and heal more rapidly than comparably severe injuries on human skin, even though human skin may be the more susceptible to injury.[12,24,27] In the rabbit, for instance, erythema becomes visible within 10 20 minutes after application of liquid H.[27]

Other differences and similarities between H burns in man and animals (rabbit, pig) have been described as follows: [12]

1. The early microscopic degenerative changes in the epidermis are similar in the three species, and human lesions of the mild and severe types bear a close resemblance to the corresponding animal lesions. Epithelium in the hair follicles is destroyed to about the same depth in man and animals, but in animals there is a greater tendency on the part of the surviving follicular epithelium to participate in the healing process.

2. Dermal injury in the form of hyperemia, hemorrhage, exudation, and necrosis is more pronounced in animals than in man. The more severe an injury in man, the more quickly does hyperemia of the central portion give way to ischemia, whereas in animals lesions of increasing severity are characterized by increasing hyperemia. A significant amount of bleeding rarely occurs from the capillaries in human skin, but in animals dermal hemorrhage is an early and prominent manifestation of injury. Exudation of white blood cells is ordinarily an inconspicuous feature of uninfected cutaneous injuries in man. In animals on the other hand, the damaged epidermis often becomes extensively undermined within 3 days by mononuclear and polymorphonuclear cells. Furthermore, the human dermis rarely reacts with necrosis of more than the more superficial layers, whereas in animals (particularly rabbits) the dermal destruction is more extensive and frequently the entire thickness is replaced by new connective tissue during the healing process.

Vesication of Animal Skin

The cutaneous injuries produced in animals by vesicants usually are not characterized by the elevated blisters that are such a prominent feature in burns of human skin. In a number of investigations, however, vesicles or vesicle-like structures have been observed in animal, bird, and frog skin following applications of H, L, or HN2.[24,25a,42,43,55,59,73a,74,94,97,103a,c,117,154,168] In some of these cases histological examination revealed that the vesicles had the characteristic intra-epidermal structure of blisters on human skin.[42,74,94,117] In other instances the epidermis remained intact and the apparent blister was merely the result of greater fluid accumulation in the corium than usually characterizes the edema of injured animal or bird skin.[42,74,103,160]

A particularly interesting example of vesication of animal skin has been observed in the regenerating epidermis of the guinea pig.[59] Thermal burns were made on the backs of guinea pigs by the application of a heated iron rod, and the epidermis was then scraped away. About 8 days later, when a scab had formed and fallen off, the regenerated epithelium was found to be considerably thickened and stratified, resembling that of man, but lacking hairs or sebaceous glands. Applications of small doses of H or L at this time produced blisters after a latency of several hours. The blisters were not accompanied by the intense dermal edema that occurs when the vesicants are applied to the normal, very thin epidermis of the guinea pig. Inasmuch as the regenerated epithelium lacked hair follicles or glands, it is obvious that the vesicants had penetrated the epithelium itself.

Intra-epidermal blisters can also be produced on the skin of the mammary gland of lactating bitches by applications of H, either as vapor or liquid.[73a,74,f] The epidermis at and near the nipple possesses a thickness and stratification similar to that of human skin, whereas away from the nipple and on most other parts of the body it consists of only one or two layers of small cuboidal cells. The epithelium of the skin of the rabbit's ear also to some extent resembles that

of human skin, and blisters have been produced upon it by applications of H and L.[76,d 134] In the case of the blisters produced by L, histological examination demonstrated that the large accumulation of fluid was intra-epidermal.[76,d] The H burns were not examined microscopically.

23.2.3 Comparison of H Burns with Thermal Burns

One of the impressions occasionally cited in the chemical warfare literature is that H burns heal more slowly than comparably severe thermal burns. It is, of course, difficult if not impossible to define or obtain equally severe burns of the two types. However, investigators of the subject during World War II have been more impressed by a similarity than by a difference in healing time between the two types of burns.[14,41f,56,115] The most obvious difference is in the latent period for production of grossly and microscopically visible damage, and there are less pronounced differences in the details of the tissue response.[13,56,115] It has also been noted that treatment with pyruvic acid and starch paste is more effective in removing the slough of the thermal than of chemical burns, and that accordingly under this treatment the thermal burns heal more rapidly.[56c]

23.2.4 Earliest Morphological Evidences of Injury

Although direct application of liquid H to living cells (e.g., in tissue culture) produces immediate coagulation or fixation,[119a] as stated above application of H to the skin is followed only after a considerable interval by gross or clinical morphological changes of a pathological nature. In animals visible injury develops somewhat more rapidly than in man, perhaps because the relatively thick keratinized layers in the skin of man impose more of a barrier to the rapid rate of penetration of applied H to the underlying living cells. In this section will be reviewed data on the earliest signs of injury in animals, as based on gross and cytological observations. Comparable cytological studies have not been carried out on human skin. The results show that evidences of injury develop within a matter of minutes after application of H to animal skin. In the following section (Section 23.2.5) additional evidence will be presented that injury demonstrable by physiological methods also develops within a matter of minutes after application of H to human and animal skin.

Clinical observation reveals the development of erythema within 10 minutes after application of H to rabbit skin;[27] the redness progressively increases, and within 1-3 hours the lesion is strongly demarcated from the surrounding normal skin by tense edema. The further course of the lesion has been described in detail.[27]

Histological and cytological observations reveal the following alterations in the skin of small mammals treated with liquid H:

1. In mice, cytoplasmic and nuclear changes were evident within 10 minutes.[26] At this time the nuclei of basal cells of the epithelium had become hyperchromatic and irregular in shape. Within 20 minutes the epithelial nuclei had become greatly shrunken and squeezed against the wall of the cells by accumulation of hydropic fluid in the cytoplasm. There were traces of dermal edema and evidence of migration of polymorphonuclear leucocytes and histiocytes. The nuclei of the dermal fibroblasts were hyperchromatic and shrunken, and the cytoplasm had become intracellularly granular. Morphological changes in the endothelium of the blood vessels were not obvious.

2. In a study on rats, changes in the epithelial cells escaped detection at 15 minutes, but the dermis was characterized by mild, diffuse edema, sparse cellular infiltration, and hyperemic blood vessels.[26] Within 1 hour the epidermal cells had become distorted and shrunken, and the dermal changes mentioned above were more pronounced. In addition, there was evidence of damage to the walls of some of the blood vessels.

3. Applications of H in an organic solvent to the skin of mice and rats were followed within 1 hour by the development of (a) altered staining properties of the mitochondria in cells of the epidermis and dermis, (b) small vacuoles in some of the basal epithelial cells, and (c) the conspicuous appearance of many lymphatics, indicative of an edematous state.[82]

23.2.5 Circulatory Changes in H Lesions

An important physiological method for the study of the properties of the smaller blood vessels depends upon the intravenous injection of blue dyes (e.g., T-1824 or Evans blue) which penetrate slowly through the walls of normal capillaries but rapidly through the walls of injured vessels. Injection of small doses of such a dye is rapidly followed by the development of blue coloration in regions where the vessels are abnormally permeable, whereas the coloration of normal regions is less intense and develops more slowly. Circulatory stasis may be demonstrated

by the injection of large doses of dye; normal areas of skin then assume a blue coloration, whereas regions in which the circulation has stopped remain colorless.

Use of this method has demonstrated both for animals and man that application of liquid H to the skin is followed within at most a few minutes by the development of abnormally high permeability of the vessels of the dermis.[27,36,94] In man there is evidence of increased capillary permeability within 10 minutes, even though detectable erythema does not develop within less than 1–2 hours.[36] In rabbits the increased capillary permeability develops even more rapidly (i.e., within 3–5 minutes or less).[27,36,94]

The intravenous injection of carbon suspensions likewise reveals that in mice the dermal capillaries have assumed abnormal properties within 10 minutes after application of liquid H to the overlying skin surface.[36] The carbon particles adhere to the endothelium in larger quantities than in normal areas of skin, indicating an increased stickiness. At a somewhat later time both free and phagocytosed particles can be seen to have passed through the capillary walls into the dermal tissue.

In spite of the rapid development of injury to the dermal vessels as revealed by their increased permeability, circulatory stasis does not develop in rabbits for 3–12 hours even in skin severely burned by application of 2.5–4.5 mg of liquid H.[27] Observations on human skin are lacking except for an isolated observation.[110b] In this instance a small drop of H was applied to the forearm and decontaminated after 10 minutes. Erythema became apparent after 1.5 hours and a blister had developed after 24 hours. The dermal capillary circulation as observed microscopically was vigorous during the stage of erythema (1.5–7 hours). It was also vigorous when examined after the roof of the blister was removed at 24 hours, and was continuing at 31 hours, after which time the lesion dried and became opaque. Presumably, circulatory stasis would be observed to develop more rapidly in the case of severe injuries characterized by coagulation necrosis.

An important and detailed study of the development of circulatory and lymphatic changes in vesicant-treated rabbit skin has been made [27] and should be consulted in the original by readers interested in this phase of the vesicant problem.

It may also be noted that injected H produces immediate vasomotor effects (see Chapter 22). These effects may or may not be identical with one or more of the actions of H which in the skin contribute significantly to the production of vesication and necrosis. In any event, denervation appears to have little or no effect on the sensitivity or response of skin to vesicants.[108,112a]

A number of investigators have shown that H blister fluid is not toxic or vesicant. In addition, it has been demonstrated that irritant substances in lymph draining from an H-treated area of rabbit skin are not sufficiently concentrated or potent to play an important role in increasing the size of the cutaneous lesion.[47]

In the classical paper in which Lewis and Grant[188] adduced evidence to show that the capillary dilatation and increased capillary permeability evoked in skin injured by mechanical and thermal trauma are due to the liberation of a histamine-like substance, it was also proposed that a similar mechanism may underlie the skin-injurant action of H and other vesicants. Lewis' concept, as well as Menkin's more recent work on biochemical units in inflammatory exudates,[188,189] have prompted further similar suggestions as well as a limited amount of experimental work with regard to the role played in the development of vesicant injuries by secondarily liberated injurious substances.[107]

In résumé, it may be stated that there is available no evidence either for or against the participation of a quickly liberated histamine-like substance. With regard to Menkin's substances, which are not believed to be identical with Lewis' histamine-like material, it has been demonstrated that a leucotaxine-like substance is present in blister fluid and in skin injured by vesicants (i.e., H and HN2).[36,94] These findings have led to the conclusion that vesicant injuries develop *because* the reaction of vesicants (e.g., H) with the skin liberates an injurious leucotaxine-like substance.[36,94] In the reviewer's opinion this conclusion, although not necessarily entirely incorrect, at least lacks foundation. The presence of a leucotaxine-like substance characterizes all types of cutaneous injury, and in vesicant injuries leucotaxine has been looked for and found only after extensive injury has already developed. That its presence or that of "necrosin" may influence the further course of injury development and healing cannot be denied. That it is the agent which directly underlies the initial development of pathological changes, however, may be questioned in the absence of any supporting evidence, particularly as the vesicants are known to react rapidly with many chemical groups of types

which are of vital importance in cells (see Chapter 19), and as the first evidences of injury (e.g., increased capillary permeability) develop within a matter of minutes after application of the vesicant to the skin. However, it has been shown that a proteinase which is quickly liberated from skin treated with H can act upon skin *in vitro* to produce leucotaxine [36,113a] (see Section 23.1.2).

23.2.6 Results of Skin-Grafting Experiments

A suggestion that the death of the epidermis following exposure of the skin to H may be secondary to dermal injury, rather than due to primary injury of the epithelial cells by H, led to the performance of the following experiments.[12] Two of four sites on each of several shaved areas of skin in young pigs were exposed to liquid H for 20 minutes and then decontaminated. Fifteen minutes later the following operation was performed, using aseptic surgical technique. One exposed site was left undisturbed as a control. The full thickness of the epidermis from the other exposed site and from the two unexposed sites was removed with a sharp knife. These grafts were then replaced in such a way as to give sites with unexposed epidermis on unexposed dermis, unexposed epidermis on exposed dermis, and exposed epidermis on unexposed dermis. The area of skin containing the four sites was then isolated as an island by curved incisions and covered with a nonirritating membrane to keep the grafts in place and protect the surface. The edges of the skin adjacent to the island were then undercut and brought together over it. This method of burying an island of skin was a modification of Harvey's technique.[41]

At least some of the transplanted epithelial cells survived in all but one of the cases in which an unexposed graft was placed on unexposed corium. Some epithelial cells also survived at least for a time in instances where an unexposed graft was placed on exposed corium, and the lamella of grafted corium was also readily capable of survival. On the other hand, the epithelium underwent complete necrosis in all instances where an exposed graft was placed on unexposed corium. It was also noted that pathological changes in the dermal tissues of the buried, ungrafted, exposed sites were considerably more severe than in the case of similar unburied control sites.

The experiments led to the following conclusions: (1) Epidermis exposed to liquid H is killed directly; its death is not secondary to any effect that H produces in the dermis. (2) A considerable part of the damage sustained by the dermis after exposure of intact skin to H may be due to the destruction of its protective epithelium. In the buried skin experiments, a new protective layer was in effect substituted for the damaged epidermis and the major dermal changes usually ascribed to primary injury by H were minimized.

23.2.7 Possible Effects of Vesicants on Intercellular Substance

British investigators [109b] have shown that perfusion of the circulation of frogs with Ringer solution containing both H and a colloid (to maintain osmotic pressure) leads after a time to the formation of edema and cutaneous vesicles. Perfusion with Ringer solution itself leads to the formation of greater edema but no blisters develop. On the basis of these observations it has been concluded [109b] that increased capillary permeability leading to development of edema is not sufficient to produce vesication, but that in addition H must produce a decrease in the resistance to the elevation of a blister by altering the properties of intercellular fibers and/or cement.

Extensive experiments which may bear on this concept have been performed on the isolated beef eye.[37b,c,d,e,f] Exposures to H vapor at dosages sufficient to produce severe clinical injury in living animals result in a marked loss in the adhesiveness of the epithelium. The loosening of the epithelium, as tested by its resistance to mechanical scraping, does not occur immediately, but only after an incubation period of several hours. It does not develop if the H vapor dosage is very great (i.e., exposure to saturated vapor for 1 hour at 22 C°). Experiments with a variety of poisons and other substances have led to the conclusion that the loosening is not based on a change in the properties of material similar to the intercellular substance of the capillary wall, but that the loosening may involve a change in the properties of the cell surface itself.

23.2.8 Résumé

The pathological findings summarized above lead to the concept that H and other vesicants exert a rapid and probably direct injurious action upon both the cells of the epidermis and the blood vessels, and presumably also upon the other cellular elements of the dermis. In part, at least, the delay in the production of gross damage is to be related to a delay in the manifestation of injury rather than to a delay in the

initial production of injury. As the lesion develops, however, injury to some parts of the skin may be accentuated as a result of the pathological changes, perhaps involving the liberation of secondary toxins, in other parts of the skin. The properties of a somewhat mysterious intercellular substance may also be involved in the mechanism of blister formation.

Data on the distribution and properties of the H that is fixed in the skin after an exposure strongly support the concepts that direct injury is sustained by the elements of both the epidermis and the dermis, and that the initial reactions which eventually culminate in gross damage are rapid. These data will be summarized after information relating to the rate of penetration of the skin by vesicants has been reviewed.

23.3 PENETRATION OF SKIN BY VESICANTS AND LOCAL FATE OF PENETRATED VESICANTS

When a drop of liquid vesicant is placed on the skin and is left uncovered, it simultaneously spreads to some extent, evaporates, and penetrates.* Only the fraction that penetrates can be of significance for injury production. Of this fraction some reacts with and becomes "fixed" by nondiffusing constituents (both living and dead) of the skin. The remainder of the penetrating fraction passes through the skin and is carried away by body fluids. Presumably that which is carried away is partly in the form of unreacted vesicant, partly in the form of hydrolytic products of the vesicant, and possibly partly in the form of vesicant that has reacted with diffusable molecules other than water. Certainly part of it is in a form that is toxic for some of the other tissues of the body (see Chapter 22).

It is very likely that cutaneous injury develops as a consequence of the fixation of the vesicant in the skin. Strong evidence for this concept in the case of Lewisite (L) is provided by the fact that the severity of cutaneous injury parallels the amount of arsenic fixed in the skin and that injury may be greatly reduced if, after L has become fixed in the skin, it is removed from its association with tissue constituents by the action of dithiol compounds (e.g., 2,3-dimercaptopropanol, BAL).[114] In the case of H there is a great deal of evidence, to be described below, that shows a correlation between severity of injury and amount of fixed H. Furthermore, all the data on the properties of fixed H and on the reactions of H with biologically important chemical groups (Chapters 19 and 21) are in accord with the concept that injury is a consequence of the fixation. It has not, however, been possible to remove fixed H from the skin by means compatible with cell life and so to determine the effect of its removal on the severity of the ensuing injury. It is highly probable that the difficultly reversible reaction of H with nondiffusible components vital to the life of cells in the skin underlies the skin-injurant action, but it should be recognized that no positive proof is available to show that other actions of the H passing through skin are not responsible for the development of injury.

The difficulty, at present the impossibility, of removing fixed H from the skin by means compatible with cell life is one of the most important generalizations emerging during World War II from studies on the mechanism of vesicant action. A second generalization of great importance is that, even after massive contamination with liquid H, *human* skin contains no appreciable amount (reservoir) of unreacted H not readily removable by surface decontamination (i.e., by treatment with H solvents such as petroleum ether). It is a corollary, supported also by direct evidence, that the reactions resulting in the fixation of H by skin constituents occur, practically speaking, almost concomitantly with exposure. Data bearing upon these two generalizations will be presented in this section in the course of a systematic summary of information bearing on the penetration of skin by vesicants and on the local fate of the penetrated molecules. Studies on the eye also show that only low concentrations are attained in the cornea on exposure to H and that at the termination of exposure the free H within the tissue rapidly disappears.[37a,45]

23.3.1 Penetration of Skin

General Observations

Calculations indicate that only a small fraction of the molecules of a vesicant vapor which strike the skin are retained by it and penetrate; the great majority are reflected back into the gas phase overlying the skin.[35a]

The effects of a liquid vesicant applied uncovered to the skin are determined not only by the intrinsic injury-producing potency of the molecules that penetrate the skin but also by the volatility of the vesicant, which determines the amount which evaporates. Volatility would not be of importance if the

* A convenient annotated bibliography on the penetration of substances (not only vesicants) was prepared in 1943.[57]

ratio of evaporation rate to penetration rate were the same for vesicants of different volatility. That this ratio differs with different vesicants, however, is revealed by the finding that the relative potencies of some compounds of widely differing volatility are different when evaporation is prevented (absolute vesicancy) than when the liquid drops are applied uncovered to the skin (empirical vesicancy).[32,35m,102,112a] (See Table 16.)

When large doses (i.e., several mg) of H or the nitrogen mustards are placed on the skin of man or animals, it is possible to demonstrate that some of the free agent persists on the skin for as long as several hours [35d,f,h,74c,f,g,h,112c,g,125b] and that in the case of H by far the greater proportion of the total dose slowly evaporates.[35d,f,112a] When small doses are placed on the skin, the contemporaneous processes of evaporation and penetration are completed more rapidly.[77a,b] The available quantitative data for human skin are summarized in Table 2. These data

TABLE 2. Evaporation of small doses of liquid H and HN3 from human skin.[77a,b]

Small doses (ca. 23 μg) of the vesicants were applied to the forearm by means of the Bensch micropipet and the amount evaporating determined by collection and analysis with suitable equipment.

Agent	Airflow velocity (mph)	No. of runs	Total amount evaporating* Per cent	Avg. dev.	Time for evaporation (min) 50%	Virtually complete
H	0.07	12	70	12	1.5	4
	0.4	11	83	11	1+	2.5
HN3	0.4	14	84	10	11	ca. 30

* By difference one may obtain the per cent retained and taken up by the skin.

for H and HN3 fail to reveal that, under comparable conditions, significantly different percentages of the two agents evaporated, but the results of tests on mice [77a,b] indicated that 50–55 per cent of the applied HN3 and about 70 per cent of the applied H evaporated under comparable conditions of flow rate and (presumably) temperature. The human data do suggest, however, that a greater fraction of the applied H evaporated at the higher of the two rates of airflow. It may confidently be expected that greater changes of airflow velocity would result in more pronounced variations in per cent evaporation.[32]

CHANNELS OF ENTRY

From time to time it has been suggested that H and the nitrogen mustards, because of their relative lack of solubility in water, must enter the skin through oily channels such as might be supplied by the secretion of the sebaceous glands in and around hair follicles. The bulk of the available evidence, however, indicates that all parts of the skin surface are penetrated by H and other vesicants:

1. H readily penetrates the continuous keratinous sheaths of feather rudiments.[110a] It also penetrates and produces vesication of areas of regenerating animal epidermis which contain no glands or hair follicles (see Section 23.2.2).

2. Radio-autographs reveal that, after exposures to radioactive H, the agent is fixed throughout the entire epidermis, not only in and about glands or hair follicles.[6]

3. The use of oil-soluble dyes [43b] and of very sensitive histochemical tests for free H [48,93,100] also demonstrate that oil-soluble molecules including H itself can, after cutaneous application, be found to have penetrated throughout all parts of the epidermis.

4. Additional suggestive evidence comes from the findings that the rubbing of lanolin into the skin (to simulate the presence of fatty sebaceous secretion) does not have much effect in altering the susceptibility of the skin to injury by H vapor.[81] On the other hand, the wetting of the skin with water or with artificial sweat, which alters the physical state of the entire cornified layer, markedly increases the susceptibility to injury by H and the nitrogen mustards.[30,81]

It may be noted, however, that none of the data suffice to determine whether the entire surface of the skin is *quantitatively* uniform with respect to penetrability by vesicants. That the region of the hair follicles (into which the sebaceous glands open) may take up more vesicant during a given exposure than the intervening areas of epidermis, or that the former regions may be intrinsically more susceptible to injury, is suggested by the occasional development of follicular erythema in the absence of a visible reaction in the intervening areas of the skin.

PENETRATION RATES

A number of studies have been made of the rates at which vesicants are taken up by the skin. In the case of H they may be conveniently but roughly summarized by the statement that the rate of penetration of human skin by the liquid or saturated vapor at room temperatures (i.e., 70 F) is of the order of magnitude of 1–4 μg cm² min. Under these conditions exposures of only a few minutes' duration suffice to produce injuries of vesicating severity.

Thus, the amount of H which must be taken up by the skin in order to produce vesication is extremely small (i.e., of the order of magnitude of 10 15 μg cm^2).

Before reviewing the data in greater detail it should be emphasized that in each specific case care must be taken to define what is meant by "penetration" of the skin.

The first quantitative study of cutaneous penetration was made by an NDRC Division 9 group at Harvard with applications of liquid H containing radioactive sulfur (S^{35}).[1,12,13] The sensitivity of the method limited quantitative determinations to relatively long exposures (i.e., 1 hour or more). However, the amount of S^{35} fixed in the skin could accurately be determined for much shorter exposures. Thus, from the latter data an estimate can be made of the penetration rate for the short times *if* it be assumed that the percentage of penetrating H that becomes fixed is the same as at longer exposure times.

In the definitive studies, liquid H in shallow, closed cups was applied for 1 hour to the abdominal skin of men, pigs, and rabbits. In each case the amount penetrating during this period was defined as the difference between the amount of H in the cup at the beginning of the exposure and the sum of the amount remaining in the cup and the amount removed from the skin by swabbing three times with cotton soaked in petroleum ether at the end of the exposure.

TABLE 3. Summary of data on penetration and local fate of liquid H applied to abdominal skin of different species for 1 hour.[12]

Species	Environmental temp (F)	Post-application period (hr)	H penetrating per cm^2 in 1 hour (μg)	Per cent of penetrated H Fixed	Extractable
Man	60	0	130	12	1 ±
		24			0
Pig	60	0	40	21	35
		24			0
Rabbit	60	0	360	8	16
		24			0
Man	102	0	330	12	1 ±
		24			0
Pig	103	0	250	24	14
		24			0
Rabbit	100	0	850	10	8
		24			0

From the data, some of which are presented in Tables 3 and 4, the following conclusions may be drawn:

TABLE 4. Penetration of human abdominal skin by liquid H as a function of temperature.[12]

The application was in shallow cups 0.43 cm^2 in area containing ca. 1.1 mg/cm^2 of liquid H.

Environmental temperature (F)	Skin temperature (F + 1)	Amount of H penetrating per cm^2 in 1 hour (μg ± 35)	(μg, avg.)
102	99	300	330
		410	
102	97	250	280
		310	
100	98.5	320	320
		320	
75	95	245	270
		280	
72	93	230	220
		220	
60	90.5	70	110
		140	
52	83.5	95	110
		130	
49	84.5	70	70
		70	

1. The average penetration rate during the 1-hour exposure was dependent upon the species and upon the environmental and/or skin temperature. The effect of temperature was more pronounced in the case of the pig than for man or the rabbit.

2. At a room temperature of 60 F, the average rates for man, the pig, and the rabbit were 130, 40, and 360 μg cm^2 hour, respectively.

3. At approximately 100 F the corresponding rates were 330, 250, and 850 μg cm^2 hour, respectively.

Similar but much less complete data indicate that the penetration rate of liquid H into pig skin remains relatively constant for exposures of up to 6 hours' duration, and that the rate of penetration of H from its saturated vapor is in the order of 0.5 1.0 times as rapid as that of the liquid at the same temperature.[1,12]

In Canadian experiments on the penetration of rat skin by radioactive liquid H [35], the skin was not swabbed with an H solvent at the end of the exposures. Instead the skin was blotted three times with absorbent paper. The data obtained under these conditions indicated that the rate of penetration was initially very rapid and subsequently fell off so that the average value was 3,100 μg cm^2 hour for the first hour and 2,200 μg cm^2 hour for the first 2 hours. The reviewer considers it probable that upon exposure to liquid H the superficial layers of the skin quickly take up an amount of loosely held H that is removed by swabbing with H solvents but not completely removed by blotting with absorbent paper.

The most thorough study of the rate of penetration of human skin by the *vapors* of vesicants has been made by applying the saturated vapors of several agents to skin of the forearm.[26] A very precise and delicate technique has been worked out and calibrated in detail.[26] It is based on determination of the amount of vesicant lost from a "penetration cup" during a period of application to the skin. Thus, the amount penetrating the skin is defined as that taken up by the skin (i.e., lost from the cup). Possible losses by evaporation from the skin after the cup is removed have not been experimentally investigated. The technique, believed to be accurate to 1 per cent, has not as yet been fully exploited and should prove to be useful in further vesicant studies, as well as in investigations on less specialized aspects of skin physiology. As originally devised and as used to date, the technique made possible determinations of the penetration rates only of saturated vapors. It has since been modified to permit studies with lower concentrations of vapor.[31]

The principal findings (Table 5) may be summarized as follows:

1. H, HN1, and HN3 penetrate the skin at the rates given in Table 5. In each case the curve relating exposure time to amount of vapor taken up by the skin from the cup was linear and passed through the origin. The penetration rates of H and HN1 for negro subjects did not differ significantly from those for whites, even though the negroes developed notably less severe injuries after exposures of a given duration.

2. In the case of benzyl β-chloroethyl sulfide a linear relation between exposure time and the amount lost from the cup was also observed but the plot did not pass through the origin. It was suggested that this might be caused by a retention on the skin surface of an appreciable quantity of the agent as a result of rapid physical adsorption or chemical combination.

3. The results with the relatively volatile ethyl β-chloroethyl sulfide showed great variation and no satisfactory value for a penetration rate was obtained. It was suggested that the skin may absorb an appreciable quantity of this agent, some of which is lost by evaporation upon removal of the penetration cup. Another complicating factor is the fact that, immediately after a 10-minute exposure, the subjects exhibited an erythema at the exposure site. With the other agents there was no immediately visible reaction.

4. The approximate V_{50}'s, i.e., the amounts of vesicant which must penetrate the skin in order to produce vesication in 50 per cent of the cases, are given in Table 5. Given also are the approximate corresponding vapor dosages calculated on the assumption that the temperature of the cup was that of the room.

In assessing these data it should be borne in mind that the penetration rates as defined were determined with high precision, although it was not determined whether any of the vapor taken up by the skin was lost as a result of post-exposure evaporation. On the other hand the V_{50}'s and the median blistering dosages were determined only approximately. The principal conclusions that may be drawn are:

1. The relation between exposure time and the amount of H, HN1, and HN3 taken up by the skin of the forearm was remarkably linear. The penetration rate for H at 70–73 F was 1.4 μg/cm²/min as

TABLE 5. Penetration of human forearm skin by saturated vesicant vapors.[26]

Agent	Room temp (F)	Relative humidity (per cent)	Number of experiments	Volatility* (mg/l)	Penetration rate and std. dev. (μg/cm²/min)		V_{50}† (μg)	Corresponding vapor dosage* (mg min/m³)	Penetration efficiency‡
H	70–73	44–46	60	0.74	1.4	± 0.06	6	3,500	1.0
	87	48–49	49	1.46	2.7	± 0.11	5	2,900	1.0
HN1	71–72	50–52	46	1.8	2.8	± 0.07	23	18,000	0.8
	86–87	47–49	56	3.3	5.1	± 0.15	26	16,500	0.8
HN3	72–73	45–48	35	0.10	0.18	± 0.01	6.5	3,700	1.0
	86	47–48	36	0.18	0.20	± 0.015	4	2,700	0.8
Benzyl β-chloroethyl sulfide	72	55–60	24	ca. 0.14	0.35	....	>34	>8,400	ca. 0.5

* Calculated on the assumption that the temperature of the penetration cup was that of the room.

† V_{50} is defined as the amount (μg/cm²) of a vesicant which must penetrate the skin in order to produce vesication at approximately 50 per cent of the exposed sites.

‡ Penetration efficiency is defined as:

$$\frac{\text{Rate of penetration of agent}}{\text{Rate of penetration of H at 70 F}} + \frac{\text{Volatility of agent}}{\text{Volatility of H}}$$

determined for exposure times of 3–30 minutes. This figure is to be compared with that of 3–4 $\mu g/cm^2/min$ for the entry of liquid H into human abdominal skin at the same temperature and under the conditions described above.

2. The penetration efficiencies of the three compounds at both temperatures were approximately the same. In contrast, on a dosage (Ct) basis the vapors of H and HN3 are much more potent than the vapor of HN1. The findings indicate that the differences in potency of these agents (and of benzyl β-chloroethyl sulfide) are to be related more to differences in the injury-producing effectiveness of the molecules that have been taken up by the skin than to differences in the ability of the agents to penetrate the skin.

3. Under the conditions of the experiments it would not appear that the skin of the human forearm is markedly more sensitive to the vesicants studied at 87–88 F than it is at 70–72 F. At the same time it is a well-established fact that hot, moist skin is definitely more susceptible to injury by given vapor dosages than is relatively cool, dry skin (see Section 23.7.2). As an explanation of the findings with the penetration cups it may first be noted that the precision with which the V_{50}'s were determined does not exclude the possibility that the skin was definitely more sensitive at the higher temperature. In fact, the data taken at face value indicate that it was somewhat more sensitive. Secondly, the higher room temperature utilized was about at, and not definitely above, the sweat point. The skin's heightened sensitivity becomes most prominent when it is actively sweating and definitely moist. Thirdly, the temperature and degree of humidification of the areas of skin covered by the penetration cups were probably not so different at the two room temperatures as would have been in the case for areas of bare skin not covered by the cups.

The experiments cited above indicate that saturated H vapor "penetrates" human skin nearly as rapidly as liquid H. This finding is corroborated at the University of Chicago Toxicity Laboratory by preliminary unpublished experiments in which an indirect measure of penetration, namely severity of resulting injury, was utilized. In the case of HN3, on the other hand, it was found that an exposure to essentially saturated vapor must be about 10 times as long as that to liquid agent (removed with a solvent at the end of the exposure) if a similar degree of injury is to result.[35a]

With the exception of some Canadian data,[132b] all penetration measurements have been made on areas exposed either to liquid vesicant or to essentially saturated vapor and covered with a glass cup. No direct measurements have been made either under conditions in which the relative humidity in the cup was maintained at a low value, or under conditions in which the skin was frankly wet. One possible interpretation of the finding that wetted human skin is markedly more susceptible than relatively dry skin to injury by the saturated vapors of H and nitrogen mustards[30] is that the vesicant vapors penetrate the wetted skin more rapidly.

23.3.2 Local Fate of Penetrated H and Free H within Skin

The most complete study on the local fate of penetrated H and other vesicants, and on the possible existence of a "reservoir" of free H within the skin, was made by an NDRC Division 9 group at Harvard.[1,12,13] This work will now be reviewed, and other findings, some of which antedated the Harvard studies, will be treated together in the following subsection.

Data Obtained at Harvard[1,12,13]

Utilizing H containing radioactive sulfur (S^{35}) having a half-life of 87 days, a study has been made in man, the pig, and the rabbit of the amount of H penetrating the skin (as described before), of the amounts of H fixed by and extractable from the exposed skin, and (by difference) of the fraction of penetrated H that is transported through the skin and carried away by body fluids to other parts of the body. The techniques have been described in detail.[12] With respect to the validity of the methods it will suffice to mention here that no evidence is available to indicate that any biological system can differentiate between isotopes. Thus, so far as the skin is observed, radioactive S^{35} until its disintegration is believed to be indistinguishable from naturally occurring isotopes of sulfur. In the most radioactive sample of H utilized, only 1 in 10^8 molecules was potentially radioactive.

The procedure for determining the amount of H penetrating the skin was outlined in the preceding section and the essential findings were reviewed. The amount of H (and reaction products thereof) extractable from the skin at any time was determined as follows. After swabbing three times with cotton soaked in petroleum ether, the skin was frozen, excised, finely ground, and extracted with chloro-

form. Subsequent manipulations of the chloroform layer served to fractionate the extractable material into H itself, thiodiglycol, and other H derivatives. The amount of H fixed in the skin was defined as the amount present that was not extractable by either cold isotonic salt solution or hot or cold chloroform, acetone, or alcohol. All measurements of penetrated, fixed, and extractable H were based on the measurement of beta particle emission due to the disintegration of S^{35} originally incorporated into the H. However, the data are always expressed in terms of the equivalent amount of mustard gas (i.e., in H equivalents).

Results of 1-Hour Exposures to Liquid H. A summary of the results for the three species is given in Table 3 and more detailed data for man are presented in Tables 4 and 6. Findings relating to penetration have already been discussed. The following conclusions may be drawn with respect to the fate of the penetrated H.

1. At the termination of the 1-hour exposure, the skin of both the pig and rabbit contained an appreciable reservoir of extractable S^{35}. In the pig about 50 per cent of the chloroform extractable fraction was H itself, about 25 per cent thiodiglycol, and about 25 per cent unidentified substances. Neither the pig nor the rabbit had detectable extractable H derivatives 24 hours after exposure.

2. In marked contrast, the reservoir of extractables in human skin at the end of exposure was negligible.

3. The fraction of penetrated H fixed at the end of the exposure was 25 ±5 per cent in the pig, about 10 per cent in the rabbit, and about 12 per cent in man. The rest of the penetrated H (i.e., 88 per cent in man) must have been carried away by body fluids before or after reaction with water or other diffusable skin components. These values were little affected by environmental temperature of 50–100 F and were essentially unchanged 24 hours after exposure. (The effect of extreme cooling and the fixation of H during the period following short exposures is discussed later in this section.) In the pig the fraction of penetrated H which becomes fixed was remarkably constant over a range of penetrated H values from 40 μg to 2.2 mg cm^2.

Thus, it appears that in the case of man, in contrast with the pig and rabbit, H is either fixed or transported almost as rapidly as it penetrates, and that the reservoir of free H present in the skin at the end of a 1-hour exposure is very small.

Fixation and Transport of H Following 10-Minute Exposures. Experiments were performed in which the exposure time was relatively short and in which the amounts of fixed and extractable H (or derivatives thereof) were followed during the post-exposure period. The results are summarized in Table 7.

The most important result was that with man, all the H that was to become fixed had done so within about 2 minutes after the end of the exposure period. At this time the amount of extractable S^{35} was of the same order as the amount that had become fixed. Even if all this extractable material were H and 12 per cent of it subsequently became fixed, the increase in total amount fixed would be negligible. Thus, *all therapeutic procedures based on neutralization of free penetrated H must necessarily be valueless, for the reason that there is no significant amount of locally free H within the skin at any time.* It has been demonstrated that this conclusion holds even when the contamination with liquid H is massive.

The situation in the case of the pig and rabbit is different. In the case of the 10-minute exposures, only about one-half of the total amount of H to be fixed has done so during the exposure period. The

TABLE 6. Fate and distribution of penetrated H in human skin — 1-hour exposures.[12]

Skin temperature (F, ±1)	Post-application period (hr)	H penetrating per cm^2 in 1 hour (μg)	H fixed per cm^2 (μg)	H fixed per cm^2 % of amount penetrating	H extractable per cm^2 (μg)*	H extractable per cm^2 % of amount penetrating
99.0	0	330	42	13	0.0	0
98.5	0	385	37	10	3.7	1
97.0	24	280	26	9	0.0	0
93.0	0	210	7?	3?	0.0	0
95.0	24	270	33	12	0.0	0
90.5	0	130	18	13.5	1.9	1.5
83.5	0	105	15	14.5	0.0	0
84.5	24	70	9.5	13.5	0.0	0
average	0	...	..	12 ± 3	..	<1
	24					0

* 1.5 μg extracted H might not have been detected, but 2.5 certainly would have been

TABLE 7. Amounts of fixed and extractable H as S^{35} in skin at various intervals after 10-minute exposures to radioactive H.[12]

Species	Post-application period	Ratio of amount of extractable to amount fixed	Ratio of amount of S^{35} fixed after stated post-application period to amount fixed after 24-hour post-application period
Man	2.0 min	0.9	1.1
	2.5 min	1.1	1.0
	3.0 min	1	1.0
	3.5 min	1.0	1.0
	10 min	0.4	1.0
	24 hr	0.0	1.0
Pig	0 min	9.3	0.4
	10 min	1.8	0.9
	20 min	1.1	1.1
	60 min	0.6	1.0
	120 min	0.3	1.0
	24 hr	0.0	1.0
Rabbit	0 min	8.8	0.5
	10 min	0.4	0.9
	20 min	0.1	1.0
	40 min	0.1	1.0
	24 hr	0.05	1.0

remaining 50 per cent becomes fixed during the first 10-20 minutes of the post-exposure period, the material being drawn from the very considerable local reservoir of H present within the skin at the termination of the exposure.

It may be noted that some extractable S^{35} remains in the skin for some time (minutes with man and hours with the pig and rabbit). Perhaps little of this represents unreacted H. In any event the fraction of it that becomes fixed does not contribute a detectable increment to the quantity of H that has already become fixed during and very shortly after the exposure.

Results of Ice-Pack Experiments. Confirmatory evidence that there is no significant reservoir of unreacted H in human skin at the end of a short exposure, but that there is a significant reservoir in pig skin, is supplied by experiments in which an ice pack was applied immediately following surface decontamination with petroleum ether at the end of 10-minute exposures to liquid H. In man (Table 8) the ice-pack treatment did not significantly affect either the amount of fixed H as determined 24 hours after exposure or the severity of the lesion that developed. In the pig (Table 9), on the other hand, the ice-pack treatment resulted in the fixation of considerably less H than would otherwise have been the case, and in the partial or complete inhibition of visible injury development. The interpretation is

TABLE 8. Effect of ice-pack treatment immediately after exposure and surface decontamination of human skin treated with liquid H.[12]

All exposures were to 1.1 mg of liquid H for 10 minutes. In each case the post-exposure period was 24 hours.

Environmental temperature (F)	Duration of ice-pack application (hr)	H fixed per cm² (μg)	Classification of injury*
70	3	0.64	I
	0	0.65	I
85	3	1.15	II
	0	1.10	II
85	3	1.9	II
	0	2.0	II
85	3	2.3	II
	0	2.5	II
85	3	5.2	III
	0	5.5	III

* I, II, and III refer to injuries of progressively increasing severity as described in detail in Section 23.3.3.

that the immediate application of ice greatly decreases the rate of fixation of H because of the high temperature coefficient for the activation of H (see Chapter 20), and that therefore the cutaneous reser-

TABLE 9. Effect of ice-pack treatment immediately after exposure and surface decontamination of pig skin treated with liquid H.[12]

All exposures were to 0.5 mg liquid H per cm² for 10 minutes. In each case the post-application period was 26 hours.

Pig No.	Duration of ice-pack application (hr)	H fixed per cm² (μg)	Classification of injury
1	6	0.22	0
		0.27	0
		0.30	±
	0	0.76	++
		0.78	++
		0.82	++
		1.0	++
2	6	0.24	0
		0.25	0
		0.34	±
	0	0.58	+
		0.62	+
		0.77	++

voir of H in the pig did not react, but rather was slowly carried away by body fluids during the prolonged period of ice-pack treatment; in man, ice-pack treatment was without demonstrable effect because practically all of the fixation occurred during exposure and no appreciable reservoir of H was present during the post-exposure ice-pack treatment. If, on the other hand, thorough surface decontamination is

not practiced, with the result that a reservoir of H exists on human skin, ice-pack treatment does reduce the severity of injury (Canadian experiments cited in reference 12).

Other Data Bearing on Local Fate of H Taken Up by Skin

In this section will be presented additional miscellaneous data relating to the fate of H taken up by the skin and to the persistence of free H within the skin. Some of the findings unequivocally reveal the existence of a small amount of free H in human skin, but none appear to compromise the principal conclusion reached above — that in human skin there is never sufficient unreacted H not removable by surface decontamination to be of practical importance in injury production.

An early observation [113] failed to reveal any free H in the skin of an amputated perfused human leg that had been contaminated with 5-mg drops of liquid H, decontaminated with charcoal paste after 10 minutes, and immediately thereafter frozen, sectioned, and extracted. Another study in which radioactive liquid H was applied to a human breast that was amputated the following day failed to reveal any S^{35} in the blister fluid.[132a] An investigation of the interaction of radioactive liquid H with excised human skin in a closed space demonstrated that after 24 hours about 50 per cent of the S^{35} applied as H was present in the skin in a form not extractable with organic solvents.[132a]

An important but indirect line of evidence, to be discussed further in Section 23.8.2, is that decontamination or early treatment with none of a large number of substances that react with and detoxify H is more effective in mitigating injuries due to liquid H than prompt, thorough surface decontamination with inert organic solvents.

The use of a sensitive histochemical test [4] that is presumably specific for H itself has been used to demonstrate the existence of free H in the skin during and subsequent to exposures to liquid H.[44,93,100] In accordance with the bulk of evidence concerning free H in human skin, the test has revealed that H is demonstrable in human (also guinea pig) skin only in the epidermis and there only for limited times after application of the liquid agent.[100] In contrast, H in small quantity was demonstrable in goat and rabbit skin for as long as a day after exposure.[100] These results with their interesting species variation were confirmed by tests in which the skin of the different species was, at various relatively long intervals after contamination, placed in contact with the human forearm.[100] Two and four hours after contamination of human and guinea pig skin with 6–10 mg of H spread over a circle 1 cm in diameter, prolonged application of the contaminated skin to the human forearm produced no injury. On the other hand, in similar experiments rabbit skin contaminated 3 hours previously and applied to the forearm for 1 hour produced an erythema; no visible injury was produced when the interval was lengthened to 1 or 4 days. However, goat skin contaminated 24 hours previously with 50 mg of liquid H produced a very faint erythema when kept in contact with a human forearm.

No explanation is currently at hand for a surprising and unconfirmed report that severe injury to rabbit skin developed as a result of contact with the skin of goats that had been heavily contaminated with H, 9 and 18 days previously.[57] The bulk of the available evidence would make it seem improbable that the cause of injury to the rabbits was a persisting reservoir of H in the goat skin.

In vitro experiments indicate that H may be reversibly adsorbed or otherwise bound by constituents of plasma [110] and by wool keratein.[113] The acetone-extracted H keratein was somewhat irritant after standing 4–6 weeks in a desiccator but ceased to be irritant after a fresh extraction with acetone. It has been suggested that a similar binding and slow liberation of H *in vivo* may have a retarding effect on the rate of healing of cutaneous injuries.[113] However, the bulk of the evidence summarized previously and in Section 23.2 leaves little reason to believe that such an effect would be of much importance.

All of the above-mentioned data and conclusions are based on studies made with liquid H. In the case of exposures to H vapor, the current consensus is that any reservoir of H which may exist in human skin after exposure to even saturated vapor also is not sufficiently large to be of practical importance, and that treatment of the skin with chloramide-containing ointments or H solvents immediately after an exposure to vapor is without significant effect on the severity of the ensuing injury.[10,24,74b]

Studies carried out during World War I,[154] however, seem to afford convincing evidence that, during short exposures to saturated H vapor, some of the agent taken up by the skin is loosely held near the

[4] Frozen sections are treated with gold chloride, which reacts with H to form an insoluble yellow complex. The latter, upon reduction with sodium hydroxide, forms a black precipitate, presumably metallic gold.

surface and evaporates subsequent to the exposure during a period of at least 30 minutes. The evidence is of two kinds. (1) Covering the skin with glass during the period following exposure to saturated H vapor resulted in more severe burns than at similarly exposed sites that were left open to the air. The augmentation increased with increased duration of the period of covering up to 30–45 minutes, and could also be observed in the case of exposed sites that were not covered until 30 minutes after exposure. (2) When an area of skin on the arm of one volunteer was exposed to saturated H vapor and then placed in contact with the arm of a second volunteer who had not been directly exposed to H, the second volunteer developed a mild burn (erythema) and the injury sustained by the first volunteer was less severe than at control sites left exposed to air after exposure. These findings are not believed to compromise, nor necessarily to be inconsistent with, the studies which, during World War II, have established the doctrine that even prompt decontamination of a vapor burn is without *practical* value. However, in retrospect it seems strange that the early studies have not been re-evaluated experimentally, and that the existence of a possible reservoir of free H in human skin after exposure to the agent as a vapor has not been subjected to direct experimental test by means of extraction tests utilizing radioactive H.

23.3.3 Properties of Fixed H and Other Vesicants

Correlation with Severity of Injury

In both man and the pig a good correlation exists between the amount of H (S^{35}) fixed per unit area of skin and the severity of the resulting injury. The correlation is not affected by differences in exposure time, environmental temperature, and other variables.

In the human experiments[12] the lesions were assessed clinically and microscopically, and the amounts of fixed H determined, 24 hours after exposure. Three major categories of injury, described in detail in Section 23.2.1, were designated as follows:

Group I *Mild injury.* This group was characterized macroscopically by erythema with or without edema and in some instances by miliary vesicles. Microscopically the principal changes were hyperemia and edema of the corium without sufficient epidermal injury to cause death of more than occasional isolated groups of basal cells.

Group II *Moderate injury.* This group was characterized macroscopically by the formation of one or more readily recognizable, isolated or confluent vesicles containing clear fluid and having erythematous margins. Microscopically the vesicles separated the epithelium from the corium. The elevated epidermis was necrotic.

Group III *Severe injury.* This group was characterized macroscopically by circumferential rather than central vesication, and by central necroses. The central area of epidermis was generally necrotic and, although there were focal areas of liquefaction, the microscopic vesicles thus formed failed to coalesce or to collect enough fluid to be macroscopically visible.

In Table 10 are listed the individual lesions in ascending order of severity within each of the three groups. It will be observed that there is excellent agreement between severity of lesion and amount of fixed H, not only among the three groups but also within each group. In rounded figures one obtains the following relationships.

Table 10. Relation between amount of fixed H per cm² and severity of resulting injury to human skin.[12] The lesions are tabulated in ascending order of severity.

Skin temperature (F)	Environmental temperature (F)	Exposure time (min)	H fixed per cm² (μg)
	Group I		
91	85	3	0.25
94	85	5	0.21
95	85	5	0.40
87	60	8	0.63
87	60	5	0.77
95	85	5	0.52
	Group II		
95	85	7	1.28
95	85	7	1.01
95	85	10	1.54
95	85	10	1.1
95	85	7	1.21
87	60	15	2.30
88.3	60	10	1.05
88.3	60	12	1.20
86.7	60	12	1.10
86.7	60	15	1.78
87.0	60	15	1.63
87.5	60	15	1.80
	Group III		
97	85	20	5.56
97	85	15	2.02
95	85	25	3.00
87	60	20	2.45
87.5	60	18	3.00
87.0	50	20	4.16

H fixed per cm² (μg)	Severity of injury
0.1–1.0	Group I
1.0–2.5	Group II
>2.5	Group III

It will be noted that both environmental and or skin temperature and individual variation markedly affected the amount of H fixed per unit time of application. Nevertheless, irrespective of these variations, it was possible to make quantitative predictions of the severity of resulting injury from the amount of H fixed.

Some of the data revealing a corresponding relationship in the pig are given in Table 9. The fixation of 0.3 0.4 μg of H per square centimeter was correlated with minimal reversible injury in the pig. The corresponding figure for man was about 0.1 μg cm^2.

Additional experiments with pigs as well as limited data for man revealed that when skin was exposed repeatedly to dosages of H, each by itself of "subinjurious" size, there was a progressive local accretion of fixed H and injury occurred *pari passu* with the attainment of levels of fixed H comparable to those producing similar injury after single, larger dosages. Representative data for the pig are given in Table 11.

TABLE 11. Correlation of severity of injury with amount of fixed H after repeated exposures of pig skin to liquid H.[12]

Liquid H was applied repeatedly to the same sites for 5 minutes at 65 F. The severity of injury was assessed and the amount of fixed H determined 24 hours after the final application.

Exposure time (min)	No. of successive applications at 24-hr intervals	Duration of ice-pack treatment (hr)	Fixed H per cm^2 (μg)	Severity of injury‡
5	1	6	0.2*	0
5	2	6	0.4†	1
5	3	6	0.3†	0
5	4	6	0.5	1
5	1	0	0.3*	1
5	2	0	0.4†	2
5	3	0	0.6†	2
5	4	0	0.75†	3
10	1	6	0.35	1
10	1	0	0.65	2
5 (80 F)	1	0	1.0	3

* Average of six experiments.
† Average of two experiments.
‡ The scale of injury (macroscopic observation) was:
0 visible reaction
1 minimal reaction
2 intermediate reaction
3 severe reaction

Furthermore, irrespective of ice-pack treatment, the severity of injury in both man and the pig paralleled the amount of fixed H (Tables 8, 9, and 11). It will be recalled that, in the pig, ice-pack treatment affected both fixation and severity of injury, whereas it affected neither significantly in man.

The one known experimental procedure that reduces the amount of H fixed in human skin is prolonged post-exposure treatment with BAL ointment, and concomitantly vesicating injuries can be converted to nonvesicating injuries.[12] This does not imply that the cutaneous injury becomes less severe, but only that character of the response is altered (see Section 23.8.3). The effect on fixed H of the treatment with BAL cannot be evaluated, for one does not know whether it resulted in the solution into the ointment of superficial keratinized epidermis containing fixed H or whether it facilitated the disintegration of substances containing fixed H in such a way that they could be carried away by body fluids. The actual splitting of the bond between H and tissue constituents is believed to be a very unlikely possibility (see Chapter 19).

The relationship between amount of vesicant fixed and severity of resulting cutaneous injury has been demonstrated semiquantitatively under a single set of conditions for several sulfur mustards in addition to H (see Table 12).[13] These agents are *bis*(β-chloroethylthio)ethane (Q), benzyl β-chloroethyl sulfide (benzyl-H), *bis*(β-chloroethyl) sulfone (H sulfone), and divinyl sulfone. In each case the results of experiments with pigs reveal a correlation between quantity of vesicant fixed and severity of injury. On the basis of number of fixed vesicant molecules per unit area of skin, the following relationships between the agents prevail:

TABLE 12. Correlation between amounts of several sulfur vesicants fixed in pig skin and severity of resulting cutaneous injury.[13]

In view of the difficulty of obtaining uniform lesions with undiluted Q, H sulfone, and divinyl sulfone, the radioactive compounds were dissolved in ethyl Cellosolve. In the case of H, use of this solvent is said not to alter the relation between amount of fixed vesicant and severity of injury.

Agent	Amount of fixed vesicant (in moles × 10^{-9}) per cm^2 of skin to produce the following types of injury		
	Mild	Moderate	Severe
Q	<1.0–1.5	1.5–2.0	>2.0
Benzyl-H	<1.0	1.0–6.0	>6.0
H	<1.0	1.0–6.0	>6.0
H sulfone	<10	10–40	>40
Divinyl sulfone	<10	10–40	>40

1. Benzyl-H and H itself are approximately equally effective. It will be recalled, in contrast, that in terms of the amount of vesicant taken up by the skin, benzyl-H is much less effective than H (see Section

23.3.1). The inference is that a smaller percentage of penetrating benzyl-H is fixed than is the case with H.

2. Q is significantly more effective than H and benzyl-H, possibly because both of the chlorine atoms in the Q molecule can react with important cell groups more frequently than is the case with the smaller H molecule.

3. H sulfone and divinyl sulfone possess only about one-seventh the efficacy of H. The divergence is not surprising inasmuch as these sulfones react by a different mechanism than H and possess different relative reactivities toward tissue groups (see Chapter 19). The similarity of the injury-producing capacity of the two sulfones is in accord with the chemical evidence that H sulfone reacts through the intermediate formation of divinyl sulfone (see Chapter 19).

Rate of Disappearance of Fixed H from Human Skin

Fixed H disappears from the skin only very slowly.[12] It remains approximately constant in amount for about a week after exposure and then slowly disappears at a rate that parallels both the rate of healing as evidenced in microscopic sections and the rate at which dead epidermis is desquamated. Thus it appears that the body cannot readily metabolize fixed H.

These statements are based on experiments with eight volunteers, each of whom received two 10-minute exposures to liquid H.[12] One site was excised after a short post-application period (1 hour to 3 days) and the other after a relatively long post-application period. The ratio of the amounts of fixed H in the two sites gives a measure of the loss of fixed H during the long post-application period. Although subject to considerable experimental error, the results (Table 13) suffice to establish the statements of the preceding paragraph.

Table 13. Rate of disappearance of fixed H from human skin [12]

Post-application period (days)	Per cent of originally fixed H still at the site
3	100
7	100
14	80
21	45
38	25

Distribution of Fixed H Within Skin

As previously stated, radio-autographs of sectioned animal and human skin treated *in vivo* with H reveal that the radioactive sulfur is fixed in all regions.[6] The epidermal concentration is significantly higher than the concentration in the corium.

Fractionation and analysis of pig skin exposed *in vivo* to liquid H likewise show that H is fixed in the cornified layer, in the malpighian layer, and in the corium.[12] The results of two quantitative experiments (Table 14) reveal that about 80 per cent of the fixed sulfur was present in the epidermis and only about 20 per cent in the dermis. Of the H fixed in the epidermis, about 70 per cent was present in the cornified layer. Since this layer consists of dead tissue, it is difficult to see how fixation of H in it could be responsible for cutaneous injury.

Table 14. Distribution of fixed H in the separated layers of pig skin.[12]

Layer of skin	μg of fixed H per cm² of exposed skin		Per cent of total fixed H	
	Expt. 1	Expt. 2	Expt. 1	Expt. 2
Total skin	2.75	5.9	100	100
Total epidermis	2.1	4.8	76	82
Cornified layer	1.4	3.5	51	59
Malpighian layer	0.70	1.3	25	23
Corium	0.65	1.1	24	18

In the case of mild to moderately severe lesions, most of the injury is confined to the malpighian layer. In the pig, fixation in this layer of about 0.25 μg of H per cm² of skin surface is associated with exposures to H sufficient to produce blisters in man. Since the number of cells per cm² of pig malpighian layer is about 2.5×10^8,[12] 10^8 10^9 molecules are fixed per malpighian cell. Although this figure appears large, it corresponds to the fixation of only about 25 micromoles of H per gram-atom of nitrogen, i.e., to the fixation of 1 molecule of H per 40,000 nitrogen atoms in the malpighian layer. Since much but not all of the skin nitrogen is in the form of protein, and since typical proteins contain only a few (i.e., approximately 4) nitrogen atoms per side-chain group potentially capable of reacting with H, this degree of injury would correspond to the reaction of H with no more than one protein side chain in 10,000.

The effects of H on cell division and reproduction (see Chapter 21) and the microscopic observations of nuclear degeneration in skin exposed to H prompted a determination of the distribution of fixed H in the nuclear and extranuclear fractions of the exposed skin.[12] Analysis revealed that an appreciable fraction (i.e., 12.5 per cent) of the fixed H was associated with constituents of the nuclei. On a nitrogen basis the

concentration of fixed H in the malpighian nuclei was only about 40 per cent of that in the entire malpighian layer (Table 15). This difference is not believed to have qualitative significance.

TABLE 15. Distribution of fixed H in the malpighian layer of pig skin: per cent present in the nuclei.[12]

Skin fraction	Micromoles of fixed H per gram-atom of nitrogen	μg of fixed H per thymonucleic acid unit	
	Expt. 1	Expt. 1	Expt. 2
Total malpighian layer	67	3.2	11.8
Nuclei from malpighian layer	37	0.42	1.45

CHEMICAL PROPERTIES OF FIXED H

The nature of the constituents of pig skin that fix H, and the character of the H-tissue linkages that are formed, have been studied.[5,12,13]

In one experiment [5,12] the skin that was used had been exposed *in vivo* to liquid H for 6 hours. Twenty-four hours later it was frozen, excised, and studied. The prolonged exposure was sufficient to produce a very severe burn. Nevertheless, the fixed H amounted to only 0.1 per cent of the dry weight of the skin and only a small fraction of the chemical groups capable of combining with H had done so. The principal findings were:

1. The treatment with H did not markedly affect the solubility characteristics of the skin constituents as revealed by a fractionation procedure simultaneously carried out with unexposed skin.

2. The H must have reacted with many different skin constituents, because there was at least a small amount of radioactive sulfur in each of the various fractions that were obtained, and because only a part of the radioactive sulfur was split off by any one of the several procedure that were utilized.

3. The fixed H was not associated to an appreciable extent with lipoidal material in the skin, for only negligible amounts of radioactive sulfur were found in acetone or alcohol-ether extracts.

4. Most of the fixed H was attached to skin proteins *not* soluble in 0.9 per cent sodium chloride solution. At least three types of linkages appear to be involved. (a) Linkages (probably carboxyl) split in the cold at a mild alkaline reaction (*p*H 9) to yield dialyzable radioactive material (principally thiodiglycol). These linkages constituted 40 per cent of the total. (b) Linkages in addition to (a) split by autoclaving to yield also dialyzable radioactive material. These linkages constituted 20 per cent of the total. (c) Linkages not split by either of the above treatments constituted 40 per cent of the total. The compounds (presumably proteins) containing this portion of the radioactive material were, however, largely brought into solution by the autoclaving procedure.

The stability of fixed H in pig skin with respect to alkaline *p*H was also studied in another experiment.[12] In this case the fixed H amounted to only about 2 μg cm² of skin surface and thus was associated with only moderately severe injury. Results obtained with skin excised after post-application periods of 1 and of 24 hours were not significantly different. The principal findings were as follows:

1. About 10 per cent of the fixed radioactive sulfur became soluble in 45 hours at *p*H 7. The percentage increased progressively with increasing *p*H and became virtually 100 per cent in 45 hours at *p*H 13.

2. About 25 per cent of the alkaline-soluble fixed radioactive sulfur was precipitated by 80 per cent alcohol. The H residues involved were undoubtedly attached to protein.

3. About 75 per cent of the alkaline-soluble radioactive sulfur was soluble in 80 per cent alcohol. Fifty to sixty per cent of this sulfur was in the form of thiodiglycol.

4. At *p*H 11 the rate of solution of fixed H became nearly negligible after 16 hours; at *p*H 9 the rate of solution was much slower.

5. Given sufficient time, 70 per cent of the fixed sulfur can be rendered soluble by treatment at *p*H values in the range 9–11. It appears to require a higher *p*H to render the remaining 30 per cent soluble.

Fractionation of skin exposed to H containing radioactive sulfur and use of the isotope dilution method might permit the identification of various of the constituents that have fixed H. Since much of the fixed H is attached to proteins, hydrolysis of the proteins in such a manner as to retain the fixed H attached to amino acid residues would permit a determination of the nature of the linkages between H and protein molecules. It has been suggested that the digestion of H-treated skin by proteolytic enzymes might achieve this end, but to date only preliminary experiments have been performed.[13]

Qualitative evidence has been obtained that the fixation of H by skin brei *in vitro* occurs by a competition factor mechanism.[12] The fraction of the H that is fixed by skin constituents is less when competing substances (e.g., thiosulfate ion) are present than when they are absent.

23.4 BIOCHEMICAL CHANGES IN VESICANT-TREATED SKIN

In this section attention will be confined principally to the metabolism of skin treated *in vivo* with vesicants, and to studies upon the activity of enzymes occurring in skin.

Most of the work on skin biochemistry in relation to H burns was stimulated by the enzyme theory of vesication (see Chapter 21). Although tentative suggestions that the action of H depends upon its reactions with proteins and/or enzymes were made early in the inter-war period,[42,112r] the enzyme theory of vesication received its greatest impetus shortly before and during the first part of World War II. It was set forth by Peters (1936)[161] in the open literature and led to a vast amount of chemical and biochemical research in the United Kingdom and the United States during the war years (see Chapters 19, 20, and 21). Its application to the arsenicals led to the fruitful development of the dithiol antidotes including 2,3-dimercaptopropanol (BAL) (see Chapters 6 and 31). No such conspicuous practical consequences for therapy have attended its application to the sulfur and nitrogen mustards. Although the theory provides a plausible interpretation for the skin-injurant action of H and related compounds, and although some but not all enzymes in the skin become inactivated as a sequel to the application of these vesicants, it remains to be determined whether or not injury is *primarily* dependent upon direct reaction of the agents with one or a few specific and highly important proteins or other molecular species which contain groups uniquely sensitive to H.[2] Alternatively, the more or less random reaction of the vesicant with the reactive groups of *numerous* proteins, which certainly occurs (Section 23.3.3), may underlie the development of the observed pathological effects.

At the present time, and without prejudice to future developments, it is probably reasonable to draw the following conclusions. (1) There exists as yet no convincing evidence that the inactivation of any one enzyme or group of enzymes has a *causal* relation to the development of vesicant burns of the skin. It is true, however, that most of the investigations have been confined to enzymes involved in carbohydrate metabolism. (2) Assuming it were found that one or more enzymes are uniquely sensitive to H and that their inactivation is causally related to the development of injury, it is not now apparent how this knowledge could be utilized to effect improved therapy (see Chapters 19 and 21). At the same time it is obvious that possibilities for investigating the causal sequence of events between the penetration and rapid fixation of H as the initial steps and the development of gross injury as the final outcome are not exhausted. A promising lead may be found in the discovery that some enzymes are *liberated* from their fixed positions in the skin as a fairly early sequel to the application of H to the skin surface *in vivo*.[23,113o]

23.4.1 Oxygen Consumption and Glycolysis

In 1935 Berenblum reported [148] that cutaneous applications of H, H sulfone, and other vesicants inhibit the development of tumors (skin carcinomas) evoked by applications of coal tar. Berenblum et al.[148] subsequently showed that H *in vitro* causes a limited inhibition of the oxygen consumption of minced tumor tissue (Jensen rat sarcoma) and a pronounced inhibition of its aerobic and anaerobic glycolysis. These observations have historical importance because they contributed to the development of the enzyme theory of vesication and led to a number of studies on skin metabolism. Most of the studies demonstrate that, subsequent to treatment of skin *in vivo* or *in vitro* with H or other sulfur and nitrogen mustards, respiration (oxygen consumption) is but slightly inhibited, whereas glycolysis is markedly reduced. In some instances skin slices were incubated with the vesicants *in vitro*.[39a,b,83] Of greater interest are the observations in which vesicants were applied to the skin *in vivo* and measurements subsequently made after excising the skin.[39c,83,109a,d,f,113d]

Aerobic Metabolism

Normal skin is an actively respiring tissue, the oxygen consumption of preparations excised from young rats being as great as 1 5 mm³/hr mg of dry weight.[109a] The resistance of the oxygen consumption to inhibition by H is revealed by the absence in one study of significant differences between normal skin and skin treated with 20 per cent H in alcohol for 1 hour when measurements were made during the first and second hours after treatment.[39c] Other observations,[109a,113a,c] however, indicate that a significant but limited inhibition of basic respiratory rate (i.e., no substrates added) does develop during the first 1 2 hours after poisoning. Oxygen consumption of untreated skin is said to be uninfluenced by addition of glucose [109a] but to be markedly increased by suc-

cinate.[113a] The per cent inhibition produced by treatment with H was decreased in the presence of succinate.[113a] In one investigation pyruvate appeared to have little effect on the respiration of the normal skin but the per cent inhibition of respiration of H-treated skin was increased.[113a] In a second study pyruvate appeared to have no effect on the oxygen consumption by normal skin.[109a] The interpretation of these findings has been debated.[109a,f,113a]

The aerobic glycolysis of normal rat skin is low and is unaffected by pyruvate.[109a] For about 1.5 hours after treatment with H there is no significant change in the rate of acid production in the presence of glucose. Within about 3 hours, however, a marked decrease has occurred, much larger than the fall in oxygen consumption, and the respiratory quotient has fallen from a normal value of 0.88 to about 0.56.[109a]

ANAEROBIC GLYCOLYSIS

The work of the Dixon group showed that under anaerobic conditions, normal excised rat skin and skin extracts in the absence of added substrate produce lactic acid at a low rate. The glycolysis of excised but otherwise intact skin is greatly increased in the presence of glucose, moderately increased by hexosediphosphate, very slightly increased by hexosemonophosphate, and not increased by glycogen.[109a] Utilization of glucose and of the hexosephosphates as well can be demonstrated in cell-free extracts if provision is made to prevent the destruction of two necessary coenzymes, cozymase and adenyltriphosphate (ATP), by enzymes present in the extracts.[109c] In acetone powder extracts from normal skin, the inactivator of cozymase is destroyed and the ATP inhibitor weakened so that it can be inhibited by fluoride. In the presence of fluoride and the necessary coenzymes, such extracts utilize glucose, glycogen (more slowly), hexosemonophosphate, and hexosediphosphate to form acids, presumably glycerophosphoric and phosphoglyceric.

After treatment with H *in vivo*, the residual glycolysis (i.e., no added substrate) of excised but otherwise intact skin remains unaltered but the glycolysis of added glucose to lactic acid becomes almost completely inhibited.[109a,f] Correspondingly, in acetone powder extracts of H-treated skin in the presence of fluoride but without added substrates, the slow utilization of ATP to yield difficultly hydrolyzable phosphorus is unaffected, but the greater phosphorus transfer which occurs in the presence of glucose is markedly inhibited, and in the presence of glycogen somewhat inhibited.[109c] With added hexosemonophosphate there is also a large inhibition of phosphorus transfer, but not so great a one as when glucose is the substrate. With added hexosediphosphate no evidence of poisoning by H is apparent.[109c]

It was stressed that the metabolic alterations just described are not apparent at 0.5–2.5 hours after application of H, but that they subsequently develop along a time course paralleling the development of gross injury to the skin.[109a,d,e,f] In addition, tests of a large number of vesicant and nonvesicant substances demonstrated the existence of a good correlation between skin-injurant action and inhibitory effect on the glycolysis of glucose by rat skin.[109a,f,117]

23.4.2 Observations and Interpretations in Terms of Enzymes in Skin

The observations mentioned above were interpretable on the basis that an important aspect of skin metabolism is, as in yeast and muscle, the breakdown of glucose by a pathway involving phosphorylating mechanisms, and that the initial phosphorylation stages mediated by hexokinase and deuterohexokinase are inhibited by H and other related vesicants. Such an important disruption of metabolism could reasonably be expected to result in cell pathology and death. It was further demonstrated by the Dixon group that yeast hexokinase *in vitro* is readily and *rapidly* inactivated by vesicants;[109d,e] that hexokinase is in fact present in the skin;[109c] that treatment of skin with H *in vivo* results in the inhibition of this hexokinase after a latency and according to a time course corresponding to those for glycolysis inhibition and the development of gross injury;[109c,f] and that zymohexase and other enzymes of the skin were not inhibited *in vivo* by H.[109c,f] These observations led Dixon to develop the hexokinase (later phosphokinase) theory of vesication.[109a,f] According to this theory a primary causal step in vesication is the reaction of the vesicant with these enzymes, which thereby become inactivated.

In appraisal of this theory it may be noted that Dixon recognized the difficulty caused for it by the evidence that H in skin rapidly undergoes activation and reaction, and does not persist as such for many minutes (Section 23.3.2). Dixon himself demonstrated that the inhibition of glycolysis develops after the usual latency even if free H is destroyed by decontamination of the skin with chloramine-T, 5 minutes

after contamination.[109a] Furthermore, important though not necessarily obvious pathological evidences of injury develop within a few minutes after application of H and other vesicants (Section 23.2.4). Thus, the available data [illegible] to warrant the conclusion that vesication [illegible] not be a consequence of the direct reaction of H with hexokinase in the skin unless implausible and complicated subsidiary hypotheses are invoked. The parallel between the time courses of hexokinase inhibition and fall of anaerobic glycolysis on the one hand and the development of gross evidences of serious injury remains striking, but it is probable that these alterations are cophenomena rather than cause and effect. In this regard some observations on the effects of BAL may be pertinent. The glycolysis inhibition produced in rat skin by H is reversed by BAL,[39a] but it is known that long-continued application of BAL, although preventing blister formation on H-treated human skin, does not prevent cell injury and death (i.e., the character but not the severity of the pathological response is altered).

In a search for early changes in H-treated skin, to which the delayed hexokinase inhibition might be secondary, it was found that there is an early liberation and disappearance of a proteinase.[112a] Fifteen minutes after heavy contamination of rat skin, in which relatively gross pathological changes appeared within a few minutes, the activity of this enzyme had decreased by over 20 per cent, and 60 minutes after the contamination the decrease in activity exceeded 40 per cent. There was evidence that much of the decrease in activity is not a direct inactivation of the enzyme as a result of reaction with the vesicant, and that the enzyme is, in part at least, liberated from its fixed position in the tissue and after a time carried away by the circulation. The steps which must precede and cause the proteinase liberation are not known. It was suggested, however, that the liberation of the proteinase, however it may be caused, may precede and cause the local appearance of leucotaxine. In any event digestion of tissues and proteins by the proteinase *in vitro* does liberate leucotaxine, and leucotaxine is produced in the skin as a consequence of treatment with vesicants.[28] As stated in Section 23.2.5, the time relations for the appearance of leucotaxine in vesicant-treated skin do not appear to have been determined, nor is evidence available as to whether the proteinase and or leucotaxine can inactivate hexokinase.

An important additional observation bearing on the liberation of enzymes in skin as a consequence of treatment with H has been made by NDRC investigators.[35] Rat skin was excised 4 hours after treatment with H and examined for phosphohexoisomerase and inorganic pyrophosphatase activity. These enzymes were chosen for test because *in vitro* the former is not inactivated by H while the latter is quite susceptible to inactivation by vesicants. The treatment with H resulted in a loss of 60–80 per cent of both enzymes from the superficial layers of the skin obtained after scraping away the edematous subcutaneous layers. However, analysis of unscraped portions of skin showed no significant differences between the isomerase and inorganic pyrophosphatase contents of H-treated and normal areas. These findings led to the suggestion that after treatment of the skin with H, these enzymes are leached from their usual positions in the skin and pass into the edema fluid of the subcutaneous layers. The edema fluid was in fact found to contain higher concentrations of both enzymes than blood serum. These observations illustrate the difficulty of interpreting the results of experiments with intact skin and must be considered in the evaluation of all the work described in this section. Furthermore, it has been emphasized that, when the *in vivo* effect of a vesicant on an enzyme in a given tissue has been established, this knowledge cannot be applied a priori to other tissues.[28]

In addition to the enzymes considered above, the possible relation of the pyruvate oxidase system to vesication has received consideration. The marked susceptibility of pyruvate oxidation in preparations other than skin to inhibition by sulfur and nitrogen mustards[112a,d,e,161] led in fact to the first serious consideration of an enzyme theory of vesication. The findings were that in chopped brain preparations the formation of pyruvate is little affected by vesicants, whereas oxidation of this acid is strikingly inhibited by H, H sulfone, divinyl sulfone, and HN3. The effect did not depend on inactivation of vitamin B_1 nor of glutathione. Although the bearing of the findings on the development of skin injury has been minimized and doubt expressed that pyruvate oxidation is of importance in the normal metabolism of skin,[107a,f] the objections in turn have been criticized.[112a]

The possible role of cholinesterase in skin metabolism and in the action of vesicants has also been considered.[112m] This enzyme is present in skin and has been found to be inactivated after cutaneous

applications of H, T, and methyl N-(β-chloroethyl)-N-nitrosocarbamate.

23.4.3 Miscellaneous Observations

Few studies have been made on the gross chemical changes that occur in vesicant-treated skin. One day subsequent to exposure to H vapor (Ct = 7,500 mg min/m³), the total phosphorus content of rat skin (pelt) was lower by about 20 per cent than in the case of fasted control rats.[73c] A further change did not occur but the concentration in the pelt of the controls progressively decreased, to become on the third day essentially the same as that in the gassed animals. The reduction involved predominantly the acid-insoluble fraction of the skin phosphorus. Under the conditions of the experiment little change in the water content of the skin was produced, and it is not known whether the early phosphorus change depended upon a *direct* effect of the vesicant on the skin.

Subsequent to application of H to rabbit and rat skin *in vivo*, no nucleoprotein was extractable, whereas a large quantity could be extracted from control areas of untreated skin.[113b]

The sodium nitroprusside test has been applied to frozen sections of normal rat skin and of skin previously treated *in vivo* with liquid H.[82] The color developed by the test in the H-treated skin was less intense than in the control skin, a finding interpreted to mean that sulfhydryl groups had disappeared as a sequel to applications of the vesicant.

The Gomori test for alkaline phosphatase is almost negative in normal skin but strongly positive in the scab of heat burns. In the case of H burns the scab and immediately subjacent tissue is negative, but regenerating dermal tissue is strongly positive.[113c]

Observations on the effects of diet on the susceptibility of skin to injury by vesicants[40] will be discussed in Section 23.7.1.

23.5 IMMUNOLOGICAL PHENOMENA AND IMMUNOCHEMICAL STUDIES

Information available as of November 1941 on skin sensitization to vesicants has been authoritatively and exhaustively reviewed.[47]

The inherent or "primary" damaging action which is exerted by H on the skin of previously unexposed men and animals presents some features in common with changes seen in eczematous allergic reactions.[47] Although it was denied by some investigators during World War I that, in addition, a specific sensitization is produced as a result of preceding exposures,[107,108] the majority of the earlier workers[47] and all of the more recent investigators[43,a,47,88,89,106,156] are agreed that sensitization develops in a considerable proportion of individuals. At the present time there can be no doubt that H, like some other simple chemical substances (e.g., dinitrochlorobenzene) can act as a potent sensitizing agent in man and also in the guinea pig.[8,43b,113d,h,126,128] Data on other species (e.g., the rabbit,[47,111] rat,[43c] and mouse[83]) are incomplete. In man and the guinea pig the acquired hypersensitivity is characterized both by skin reactions to dosages to which "normal" individuals do not react and by more definite reactions to larger dosages than are exhibited by normal individuals.

23.5.1 SENSITIZATION IN MAN

Localized exposures to H appear in many cases to be followed by an increased sensitivity of the body surface as a whole in man as well as in the guinea pig,[8] but it is possible that a greater degree of hypersensitivity develops in the neighborhood of a previously burned area than at more distant regions of the body.[43d] In experiments in which subjects were exposed to localized applications of liquid H, cutaneous hypersensitivity could be demonstrated within 8 days but was more pronounced after 4 weeks. The acquired hypersensitivity appears to persist for long periods and perhaps for life.[47,108] Results of animal experiments[8,126] are in accord with this view and it may be noted that a worker who appears to have developed a hypersensitivity to H during World War I exhibited an extreme degree of sensitivity when he again encountered the agent during World War II.

The reactions of hypersensitive individuals to test applications of H in small doses frequently are characterized by the delayed development of erythematous, papular, and vesicular lesions. This form of response, similar to those evoked by eczematous allergens such as poison ivy and certain dyes, is believed by some authorities to be typical of hypersensitivity to H.[47] The flare-up of old, healed H lesions after fresh contamination of another site has also frequently been observed.[47,130] Flare-up may manifest itself as itching, as erythema and edema, or even in some instances as full-blown vesication. In addition to the usual eczematous sensitizations, there have been reported two cases of urticarial sensitization. In these instances wheal formation developed

a short time after application of H to subjects who had previously been exposed to the agent.[47,115]

In various investigations the incidence of hypersensitivity subsequent to exposure to H, as tested by applications of small amounts of H diluted in a drop of solvent, has varied between about 30 per cent and about 65 per cent.[47] Degrees of sensitivity 1,000 times greater than the "normal" as determined by drop dilution tests develop in a few instances.[88,89] It is difficult, however, to estimate in how large a percentage of cases the hypersensitivity becomes sufficient to bear practically on the field aspects of chemical warfare. It is clear, in any event, that a small proportion of individuals do develop such high degrees of hypersensitivity [47] and a few apparently possess such exceptional unconditioned sensitivity,[187] that it is impractical for them to work in laboratories or factories where H is present in such small concentrations as to be without apparent effect on the majority of workers.

A striking example of extreme sensitivity to H vapor is supplied by a recent incident at Edgewood Arsenal.[70] A soldier who had previously experienced severe reactions from exposure to small amounts of chemical warfare agents and who was known to suffer from hay fever was accidentally exposed to a small amount of H vapor which drifted over the area in which he was quartered. Although normal subjects in the same area experienced no symptoms and although two other H-sensitive individuals developed only slight reactions, the soldier in question developed sufficiently severe systemic symptoms and cutaneous injuries, including extensive, intense edema and areas of vesication, as to require hospitalization. Some of the skin lesions required 28 days to heal.

One instance of acquired cutaneous hypersensitivity to a nitrogen mustard (HN3) has been described.[188] There is also one reported case of noncutaneous sensitivity to HN1, in which slight exposure to the vesicant caused allergic conjunctivitis and acute asthmatoid bronchitis.[56] The subject was not exceptionally sensitive to H or L. It is not known whether the relative absence of reports on cutaneous sensitization to nitrogen mustards reflects low sensitizing potency of these compounds or merely the fact that relatively few subjects have been exposed, and in particular repeatedly exposed, to these agents.[47]

There is good evidence that sensitization to H is not associated with increased susceptibility to arsenical vesicants.[47,77c]

23.5.2 Sensitization and Desensitization in Guinea Pigs

Under NDRC auspices an investigation of the development and possible prevention or abolition of hypersensitivity to H was initiated very early in the war and led to what appear to have been the first experimental sensitizations of laboratory animals to this agent.[8] The results together with those of simultaneously and subsequently conducted American,[43b] British,[121,8,9,117] and Canadian [126,124] studies will be reviewed in this section. It may be noted that the active NDRC work in this field was discontinued late in 1942 because it was believed that no information of practical importance to the military during the war would result from additional short-term studies. Although partial desensitization and refractoriness to sensitization have been produced in guinea pigs, the studies have not been extended to human subjects, and the results, although interesting and provocative, do not suggest practical procedures for protection against H in warfare.

Induction of Hypersensitivity

Definite cutaneous hypersensitivity to H in guinea pigs has been produced quite consistently by the following procedures:

1. Treatment of the skin of the back with 8 drops of a 0.05 or 0.10 per cent solution of H in ligroin about 10 times during 3 weeks.[8] Two to 3 weeks after the final application almost all of the animals reacted to a test (application of 0.1 per cent H in castor oil) which in normal control animals was consistently negative. The animals reacted as vigorously and consistently to tests with highly purified (recrystallized) H as to less pure thiodiglycol or Lewinstein H. The sensitizing applications of 0.05–0.10 per cent H elicited considerable inflammation of the skin. Sensitizing application of 0.02 per cent likewise elicited inflammation and induced hypersensitivity, but 0.004 per cent H caused relatively little inflammation and practically no hypersensitivity. Six applications of 0.5 per cent H in ligroin, which caused severe burns, proved less effective than the more numerous treatments with 0.05–0.10 per cent solutions. Animals burned severely with a single drop of undiluted H likewise developed hypersensitivity of only a low degree. Repeated exposures to dilute H vapor elicited slight hypersensitivity in some animals but not in others.

2. Treatment with 0.15 per cent H in ligroin once daily for 10 days.[43] Some but not all animals pre-

viously given a single small dose of H also exhibited hypersensitivity.

3. Intraperitoneal injection of formalin-killed tubercle bacilli, followed 1 day later by intraperitoneal injection of 0.1 mg of H.[112d]

4. Scalding of the skin sufficient to produce edema without ulceration, followed 1 day later by intraperitoneal injection of 0.4 mg of H.[112d]

5. Repeated applications to the same spot on the skin of small doses of H diluted in benzene.[112d,k] This method produced generalized hypersensitivity over the body surface but the site where the sensitizing applications had been applied was distinctly more sensitive. It was considered that this procedure is the simplest and most effective method for sensitizing guinea pigs to H.[112k]

6. Daily application for 10 days to the same portion of the skin of 2 drops of 0.1 per cent H in dry benzene.[128] As in (1) above, a single severe burn with H was followed by the development of hypersensitivity, but only of a low degree.

Taken as a whole, the observations demonstrate that in the guinea pig hypersensitivity is most effectively produced by repeated applications of H in doses which, though relatively small, are sufficient to produce skin injury. One or a few larger applications are less effective.

Degree and Time Course of Hypersensitivity

The degree of hypersensitivity, as tested by the evocation of threshold responses to dilute H solutions 2 3 weeks after the end of a course of sensitizing applications, is considerable. In one investigation [112k] the erythema-producing dose for normal control animals was 1 μg of H in benzene. The hypersensitive animals reacted to about 0.2 μg, indicating a 20-fold increase in sensitivity. In another investigation [128] control animals reacted to H at a maximum dilution of 1 1,000 to 1 2,000 in benzene, whereas a sensitizing course of applications was followed in the majority of animals by reaction to a dilution of 1 32,000.

The time of onset of hypersensitivity has not been investigated quantitatively but there is evidence that it is present to a significant degree within 10 days after the start of a sensitizing schedule.[128] All investigators [8,112e,128] agree that hypersensitivity, once established, persists unchanged for prolonged periods. In one instance the reactions of animals tested 22 months after sensitization were not significantly less pronounced than the reactions of the same animals 2 3 weeks after sensitization.[8]

Specificity of Sensitization

Several guinea pigs markedly hypersensitive to H failed to react either to *bis*(β-chloroethyl) ether or to thiodiglycol applied to the shaved skin.[8]

In another investigation animals hypersensitive to H proved to be hypersensitive to propyl β-chloroethyl sulfide, N-heptyl β-chloroethyl sulfide, and to β-ethoxy chloroethyl sulfide (*sic*), but not to phenyl β-chloroethyl sulfide, H sulfone, or HN2.[112k,117]

Relative Susceptibility of Hypersensitive and Normal Guinea Pigs to Severe Injury by H

It is important to know whether large ("casualty-producing") applications of H produce more severe or more prolonged injury in hypersensitive than in normal animals. The limited available data indicate that the differences are not great.[8] The onset of marked injury appears to be somewhat more rapid in the sensitized animals and can be evoked by slightly smaller doses of liquid H, but in general the severity and healing time of severe injuries in the two classes of animals are not very different. Hypersensitive animals proved to be little if any more susceptible to the effects of inhaled vapor than did normal controls.

Prevention of Sensitization to H

Partial refractoriness to sensitization to H has been produced by a variety of procedures:

1. Guinea pigs repeatedly exposed to very small dosages of H vapor and subsequently subjected to a "sensitizing" schedule of cutaneous applications of H in ligroin usually failed to develop as pronounced a degree of hypersensitivity as was obtained with normal animals.[8]

2. Partial refractoriness to full sensitization by H was also induced by prior treatment with a series of applications of highly diluted H in ligroin (i.e., concentrations lower than those which produce injury and induce hypersensitivity).[8]

3. Guinea pigs that had sustained a severe burn due to liquid H and were subsequently given a "sensitizing" schedule of cutaneous applications of H in benzene developed considerably less hypersensitivity than normal control animals.[128]

4. A similar result was obtained when the conditioning application of H, instead of being very large and productive of severe injury, was only a minute dose (10 μg) given some 6 weeks antecedent to the sensitizing schedule.[128] Subsequent to the sensitizing schedule, 11 of the unconditioned animals reacted to a maximum dilution of 1 32,000 H in benzene and

3 to 1/16,000, whereas of the conditioned animals 15 of 16 reacted only to maximum dilutions of 1/8,000 or less.

5. There is some evidence that previous immunization with diptheria toxoid may reduce the capacity of guinea pigs to be rendered hypersensitive to H by the usual procedures.[113a]

Desensitization

The only procedure which has resulted in significant desensitization of hypersensitive guinea pigs has been the prolonged daily administration of H in small doses to the skin.[128] In one experiment a group (A) of animals received daily for 10 days 2 drops of 0.1 per cent H in petroleum ether. A second group (B) received these doses and in addition 20 daily administrations of 0.02 per cent H in petroleum ether. The skin responses of both groups at 10 days indicated that all animals were becoming sensitized. However, 2 weeks after the completion of the course of injections given to group B, it was found that in this group, 1 animal reacted to a maximum dilution of 1/8,000, 9 to 1/4,000, and 1 to 1/2,000, whereas in group A, 6 reacted to 1/32,000 and 2 to 1/16,000. In a second experiment hypersensitive animals were treated daily for 30 days with a drop of 0.02 per cent H in petroleum ether. Before the course, 3 of 6 reacted to a maximum dilution of 1/32,000 and 3 of 6 to 1/16,000. After the course, 2 of 6 reacted to a maximum dilution of 1/16,000, 3 of 6 to 1/8,000, and 1 of 6 to 1/4,000.

Attempts to desensitize hypersensitive animals by the following procedures have not met with success: repeated intraperitoneal injections of H in olive oil, repeated exposures to low dosages of H vapor, intraperitoneal injections of H-treated proteins, and cutaneous applications of *bis*(β-chloroethyl) ether or of thiodiglycol;[8] production of a severe H burn, intraperitoneal injection of H in sesame oil, an immunizing schedule with an H-serum conjugate, and intraperitoneal injections of a potent antiserum against a conjugate of H with serum globulin;[128] and feeding of H-treated keratein or of powdered skin from H-sensitive guinea pigs.[113a] The effects of ingestion of H in olive oil were erratic in a small series of tests.[113a]

23.5.3 Miscellaneous Observations

Of interest in relation to various miscellaneous observations and to future work on sensitivity and hypersensitivity to vesicants are a number of studies on the preparation and chemical and immunological properties of H-serum protein complexes.[109b,123,125,127,147] H-serum protein complexes prepared in phosphate buffer contain residues of phosphate as well as of diethyl sulfide and protein.[127] Injection of H-serum protein complexes produces antibodies which give precipitin reactions with the antigen injected.[109b,126,147] Similar observations have been made with antigens prepared by treatment of serum protein with H sulfone and divinyl sulfone.[109b,147] There is cross-reaction between proteins treated with the two sulfones, but not between sulfone-treated and H-treated proteins[109b] — an observation of historical interest in relation to the "sulfone theory" of the action of H.

Implantation of an H-collagen complex under the skins of rabbits evoked no particular reaction,[111] nor in normal guinea pigs did intradermal injection of an H-serum protein conjugate.[126] In some hypersensitive guinea pigs, however, injection of the H-serum protein complex evoked a severe delayed reaction consisting of an area of marked erythema and edema with central necrosis.[126]

No anaphylactic symptoms were observed in H-sensitized guinea pigs upon intravenous injection of H-protein complexes.[126]

The limited available evidence would seem to indicate that a skin site on a normal human subject is not sensitized to the injury-producing action of H by intradermal injection of serum from a hypersensitive individual,[73a] although the possible existence of such passive sensitization had been suggested by earlier observations.[67]

23.6 MOLECULAR STRUCTURE IN RELATION TO VESICANCY

In order to produce vesication a substance must (1) be brought into contact with the skin, (2) penetrate into the skin, and (3) there exert actions that culminate in injury.

The readiness with which a substance may practically be brought into contact with the skin has little bearing on the *mechanism* of vesication but is of great practical importance in the choice of a vesicant for use in warfare. Numerous physical and chemical characteristics (i.e., ease of synthesis, physical state, vapor pressure, stability, susceptibility to hydrolysis, etc.) play a role and consequently require consideration in evaluations such as those presented in Chapters 5 and 6. It will suffice here to mention two generalizations. First, a solid vesicant (e.g., crystal-

TABLE 16. Vapor pressures and vesicancies of some sulfur mustards.

Compound	Vapor pressure (mm Hg at 20°C)	Median vesicating dose (μg)*	Absolute vesicancy in relation to H = 100†
β-Chloroethyl mercaptan	18[51]	....	<3[10,51]
Methyl β-chloroethyl sulfide	5.4[19]	>200[32]	0[10,106]
Ethyl β-chloroethyl sulfide	2.4[19]	>200[32]	0[10,103,106]
H	0.75[19]	32[29]	100
T	0.00015[36]	4[29]	<100[102]
Q	0.000013[36]	0.3[29]	100–200[103]

* Liquids applied uncovered to skin; the Q was dissolved in dioxane.
† Liquids applied to skin and covered to prevent evaporation, or skin exposed to known dosages (CT's) of vapor.

line Q) of great intrinsic potency may in practice prove to be relatively ineffective when applied to bare, dry skin, because it makes poor contact and is apt to be rubbed or blown off before it penetrates.[35] Second, if one compares H with the most vesicant sulfur mustards having either much higher or much lower vapor pressures, there appears (Table 16) an inverse correlation between vesicant potency and vapor pressure. Thus, the most vesicant compounds cannot be utilized at high vapor concentrations.

With regard to penetration of the skin, some substances (e.g., iodine, methyl salicylate) which readily penetrate lack vesicant properties. Other substances which are potent cytotoxic agents when introduced into the body are relatively innocuous when applied to the skin, presumably because they are poor penetrants. The sulfonium salts of H provide one example. Another interesting example is supplied by a comparison of H with its selenium analog, *bis*-(β-chloroethyl) selenide; the two agents possess approximately the same toxicity as measured by their $LC(CT)_{50}$'s for mice, but the selenide would appear to be at least several times less potent than H as a vesicant.[16]

Among the vesicant substances, quantitative data on rate of penetration are available only for H, benzyl-H, HN1, and HN3 (see Section 23.3.1). It is noteworthy that the vapors of these four substances which differ considerably in physicochemical properties are taken up by the skin with approximately the same efficiency (see Table 5). Thus, the differences which they exhibit in vesicant potency must be due to differences in the injury-producing effectiveness of the molecules that have penetrated into the skin.

The distribution, activation, and reaction of vesicant substances in a heterogeneous system such as the skin are so complicated that no detailed rational interpretation of vesicant potency in relation to physical and chemical properties can as yet be made for any series of chemically related compounds. This situation prevails for the sulfur and nitrogen mustards in spite of detailed studies on the nature and kinetics of their chemical reactions (Chapters 19 and 20) and on their toxicology (Chapters 5, 6, 21, and 22). The meager results of attempts to correlate kinetic data with toxicity are summarized in Section 22.8. Perusal of the reports cited in Section 23.3 will reveal how difficult it has been to obtain for only a few compounds some of the quantitative toxicological information that would be required, and attention has been called to precautions that should be observed in comparative studies.[102]

There are available, however, the results of vesicancy screening tests with numerous sulfur and nitrogen mustards and related compounds (see Tables 1 of Chapters 5 and 6).[16,23,32,88,102,103,105] From these data it has been possible to derive for the sulfur compounds a number of empirical correlations between molecular structure and vesicancy.[4,30b,105] Some of the more general conclusions follow:

1. β-Chlorothioethers are the most effective vesicants among sulfur compounds. Change of position of the chlorine atom causes vesicant action to fall off sharply.

2. The vesicant power is greatly decreased if the chlorine atom is replaced by an iodine atom or by a group such as cyano, thiocyano, acetoxy, or oximino.

3. Introduction of a substituent on a β-chloroethylthio group of a vesicant decreases or destroys its vesicant action.

4. The vesicant power of a thioether is decreased by any change in structure which lessens the basicity of the sulfur atom.

5. Q and its homologs having the general formula $ClCH_2CH_2S(CH_2)_nSCH_2CH_2Cl$ are more vesicant than H when $n = 1$ 5; the vesicancy drops off markedly for higher values of n.

6. β-Chloroethyl disulfides are only very slightly vesicant.

7. Compounds of the type $ClCH_2CH_2S(CH_2)_nS(CH_2)_nSCH_2CH_2Cl$ are less vesicant than H.

8. Compounds containing the >SO group, such as sulfites and sulfoxides, are not vesicant.

9. Certain β-chloroethyl and β-bromoethyl sulfones, sulfonyl chlorides, and sulfates are vesicant.

10. Vesicancy is also exhibited in lesser degree by certain halogen-free sulfones and sulfates.

11. All of the highly vesicant compounds possess considerable lipoid solubility.

It may be noted in conclusion that the chemical mechanism of activation and reaction is different for the sulfones (e.g., divinyl sulfone) than for the more typical β-chloroethyl sulfur and nitrogen mustards (Chapter 19), and that the N-β-chloroethyl-N-nitrosocarbamates (Chapter 8) and the arsenicals (Chapter 7) act by still other mechanisms.

23.7 FACTORS INFLUENCING INJURY-PRODUCING EFFECTIVENESS OF VESICANTS

The injury-producing effectiveness of H and other sulfur and nitrogen mustards is influenced by a multitude of biological and physical variables. All these variables should be considered in the planning and interpretation of quantitative studies on the mechanism of vesication. Many of them bear importantly on the effectiveness of vesicants in the field. The factors that have been correlated with susceptibility will first be listed and discussed empirically (Section 23.7.1), with the understanding that correlations do not necessarily imply direct causal relationships. A brief attempt will then be made to integrate the findings and to define some of the variables that appear to be of primary importance (Section 23.7.2).

23.7.1 Factors Correlated with Susceptibility

Species

It is clear that species differences in susceptibility to cutaneous injury by H as vapor and liquid exist [12,24,32,90,116,147] but there does not appear to have been occasion to make extensive comparative studies. The order of susceptibility might not prove to be invariant under various testing conditions. There is agreement that the horse is relatively sensitive,[116,147] and the guinea pig and monkey appear to be relatively resistant.[32,147] Some observers [12] consider the rabbit sensitive relative to man, but under different conditions others [24] have found it more resistant even though injury develops more rapidly than in man. The pig is a convenient experimental animal when human subjects cannot be used.[12,24]

In addition to differences in susceptibility to injury, there are marked species differences in the character and time course of injury development and healing (see Section 23.2).

Race, Pigment, and Complexion

A number of observations demonstrate that negroes are more resistant than whites (Caucasians) to H as vapor and liquid.[32,42,131,147] A similar difference is revealed by less extensive data for HN2 (Table 17)

TABLE 17. Relative susceptibility of negroes and whites to small doses of liquid H and HN2.[28]

Agent	Dose (μg)	Race	Erythemas	Blisters
H	65	White	38/38	32/38
		Negro	20/30	8/30
HN2	170	White	26/35	6/35
		Negro	8/30	0/30

and HN1.[28] In the case of HN1, tested by localized applications of saturated vapor, the results indicate that the ratio of the exposure times to produce equal injury in the two races may be in the order of 1/3 or 1/4.[28] The ratio in the case of H does not appear to be greater and may be less.[28] In spite of this significant racial difference in susceptibility to injury, the vapors of H and HN1 penetrate the skin of negroes equally as rapidly as that of whites.[28] It has been suggested that the relative resistance of negroes may be related to the relatively thick horny layer of their skin.[47] There do not appear to have been man-chamber or field tests to determine whether the *casualty-producing* effect of H in negroes is sufficiently less than in whites to be of practical significance in warfare.

In view of the apparently well-established difference between the susceptibility of negroes and whites when tested in temperate climates, it is of interest to note that little difference was found between the severity of injuries produced by application of small amounts of liquid H to Puerto Rican troops and to troops from the continental United States.[47] Both groups of subjects were acclimated to the tropics. The development of vesication in the Puerto Ricans tended to be slower but the difference was not established with statistical significance.

An extensive series of tests has been conducted to determine the relative sensitivity of white and

Japanese-American (Nisei) troops in the United States Army.[36b,43b,72] No significant differences were found between the reactions of the two groups either to liquid H at small doses or to vapor at dosages of 75 and 150 mg min/m³.

Some observers have reported that, among whites, fair-complexioned individuals react more severely to H than darker-skinned subjects [118,131] but others have failed to note conspicuous differences.[47]

Data on the relation in animals of pigmentation to susceptibility to H are not consistent. In a black and white piebald pig no difference in susceptibility of pigmented and nonpigmented areas was observed.[12] In piebald rats, on the other hand, it is reported that liquid H produced larger and deeper burns in the pigmented areas than in the nonpigmented regions,[40a] whereas light-skinned guinea pigs appeared to be decidedly more sensitive to mild injury by H vapor than dark-skinned animals.[43]

Individual Variation

The errors inherent in testing methods as well as the action of spurious environmental variables undoubtedly have contributed to the commonly held impression that normal (i.e., not previously exposed) individuals differ enormously in their sensitivity to H. Nevertheless, there can be little doubt that considerable and, rarely, large variations in susceptibility to injury do exist between individuals of a group that is apparently homogeneous with respect to the variables enumerated above and below. The pertinent literature on man and animals was reviewed in detail in 1944. In addition to the more important papers evaluated in the review [43,50,106,131,137,167] the results of a few other studies are available.[14,26,32]

In one group of previously unexposed individuals, relative sensitivity to H was found to be definitely correlated with susceptibility to HN3, slightly correlated with susceptibility to Q and T, but not correlated significantly with susceptibility to L or phenyldichlorarsine.[77c]

Acquired Hypersensitivity

Exposure and, particularly, repeated exposure to H often leads to the development of acquired hypersensitivity (see Section 23.5).

Part of Body

One of the most striking facts about susceptibility to H and the nitrogen mustards is the existence of pronounced differences between the various regions of the body, at least under conditions when there is not generalized sweating. The numerous pertinent data from man-chamber and field tests have recently been summarized.[81,82,88,137] In general the most sensitive regions are those that usually are warm and moist and/or subject to friction.[47] These areas include the scrotum, penis, axillae, and the cubital and popliteal fossae. However, the palm of the hand is exceptionally resistant.[91] Regional differences still exist but are much less pronounced when the body surface as a whole is wet with sweat.[81,144]

Regional differences in sensitivity have been observed in animals as well as in man.[12,40c,43a] (See also Section 23.2.2.)

Age and Size

Within the rather limited age range of 17–35 years, no correlation of susceptibility with age of human subject has been found in tests with several sulfur and nitrogen mustards, namely H, HQ mixture, T, HN1, and HN3.[77c]

It has been reported that ducks 9 weeks old are definitely more sensitive to injury by small doses of liquid H than ducks 18 months old.[42,160]

Nutritional State

There appears to be no evidence that either susceptibility to injury by H or time for healing of H injuries are appreciably affected by specially fortified diets or by subclinical nutritional deficiencies. However, a series of studies [40] on the severity and healing time of burns produced by liquid H in rats demonstrates that alterations can be produced by certain *extreme* nutritional deficiencies, whereas certain other variations in diet are without effect. The findings may be summarized as follows.

1. Nutritional deficiency apparently resulting in less extensive injury than in normal rats: advanced biotin deficiency characterized by generalized exfoliative dermatitis.[40n]

2. Nutritional deficiencies having little or no effect on extent of injury or time for healing: carbohydrate deficiency;[40h] moderate protein deficiency;[40f] vitamin A deficiency;[40p] and magnesium deficiency characterized by erythematous and edematous skin.[40q]

3. Nutritional deficiencies resulting in increased extent of injury and duration of healing time: severe fat deficiency characterized by an atrophic, scaly, inelastic skin;[40g] severe protein deficiency;[40i] severe deficiency of the entire vitamin B complex except thiamin, characterized by an atrophic, thin skin;[40d]

moderate biotin deficiency;[40e] pyridoxine deficiency;[40k] riboflavin deficiency;[40l] pantothenic acid deficiency;[40m] and, possibly, severe inanition.[40n]

4. Additions to a normal, complete diet having no effect on extent of injury or on time for healing: thiamin;[40c] riboflavin;[40l] pyridoxine;[40f] pantothenic acid;[40f] nicotinic acid;[40f] inositol;[40f] para-aminobenzoic acid;[40f] biotin;[40e] choline;[40n] cystine;[40n] and (when administered only subsequent to the application of H) vitamin A concentrate.[40w]

5. Dietary alteration having no detected effect: substitution of para-aminobenzamide for para-aminobenzoic acid.[40m]

Acclimatization; Pre- and Post-Exposure Conditioning

There is a general impression that, independent of ambient temperature and humidity, the skin is less sensitive to injury by H in the winter than in the summer in temperate climates, and that acclimatization to the tropics may alter susceptibility. However, evidence bearing on these suppositions is limited and apparently conflicting. Ambient temperature and humidity were not adequately controlled in some of the earlier observations.[81] Moreover, measurement of ambient temperature is an incomplete measure of thermal environment; the radiant energy component has been overlooked in all work to date.

Two thorough investigations at the University of Chicago Toxicity Laboratory[14,76] fail to reveal any difference in intrinsic sensitivity to H in summer and winter at Chicago. The first of these investigations was a statistical analysis of extensive data obtained with liquid H in small doses.[14] No evidence of a cumulative seasonal effect independent of ambient temperature and humidity was apparent. The second[76] was an extensive series of man-chamber trials in which subjects were exposed to H vapor at a dosage of 100 mg min m^3 at various chamber temperatures and humidities. Exposures during February and March (cool weather) produced neither more nor less severe burns than exposures at corresponding chamber temperatures and humidities during July and August (hot weather).

On the other hand observations at the United States Naval Research Laboratory reveal that exposure of subjects to the vapors of H, HN1, and HN3 under controlled conditions in a man-chamber leads to somewhat more severe injuries in summer than in winter.[81,82] Evidence was produced that preconditioning the subjects immediately prior to a 60-minute exposure period definitely decreased the severity of injury, and it was suggested that this factor might underlie the observed seasonal effect. In any event it is apparent that adequate evaluation of a possible effect of acclimatization on sensitivity requires that the subjects be maintained at a chamber temperature and humidity for a short while before and after the actual exposure to vesicant vapor if the outside conditions are greatly different from those in the chamber.

This condition was fulfilled in the course of limited arm-chamber observations with HN1 vapor.[80] The results indicated that at a temperature of 90 F and relative humidity of 65 per cent this agent produced definitely more severe injuries in the summer than during cool fall weather.

Some Australian observations also seem clearly to reveal an effect of either pre- or post-exposure conditioning.[131,132] Exposure of subjects to H vapor at the beginning of the hot season resulted in definitely more severe injuries than comparable exposures at the same ambient temperature and relative humidity at the end of the hot season. The tentative interpretation given in the original report,[132] that the more severe effects produced at the beginning of the hot season is to be related to the higher environmental temperature prevailing during the post-exposure period, is plausible. Logically, however, there exists the alternative possibility that the difference in susceptibility was related to differences in pre-exposure meteorological conditions or in the activities of the subjects during the hours, days, or weeks before their exposure.

It has generally been assumed that post-exposure physical exercise, by producing mechanical chafing and trauma to partially injured skin (e.g., of the scrotum), increases the severity of vesicant injuries.[81,85] However, in actual tests Australian investigators have noted no marked differences in severity of injury or time for healing between burned volunteer subjects who engaged in daily assault course runs and others who undertook no violent exercise.[132]

State of Vesicant

A vesicant may be applied as vapor, as liquid in large drops or splashes, or as a particulate of varying (small) particle size. Comparisons of the effects of liquid and vapor have been made in the preceding sections of this chapter and the characteristics of par-

ticulate clouds of vesicants[35j,n,o,p,77a] are discussed in Chapter 15.

The size and severity of the injury produced by a given amount of liquid vesicant (e.g., H) is affected by the degree to which the liquid is spread over the skin. This in turn may be affected either by the mode of application[21,43b] or by movements of the subject or animal to which the dose is applied.[10w]

Dosage

The time that a liquid vesicant remains in contact with the skin and, in the case of vapor, the dosage (Ct) to which the skin is exposed are prime factors in determining severity of injury. The numerous available man-chamber and field test data suffice reasonably well to define the effects of exposure to various dosages of H vapor on totally exposed human subjects under various conditions[70,76,91,134,138,139,142,144] and have recently been summarized and reviewed.[36] Similar but less extensive data are also available for the nitrogen mustards.[37] Data and calculations on the dose-lesion relationship for vesicants as vapors and liquids applied to small areas of skin are also available.[12,15,18,20,29,32,80]

Exposure Time; Multiple Exposures

Data on the $L(Ct)_{50}$'s of H and on the eye effects of H and the nitrogen mustards give clear evidence of deviations from Haber's law for the range of exposure time 10–240 minutes (see Chapters 5 and 6). Although early observations also suggested the existence of pronounced variation in blistering dosage (Ct) of H vapor as a function of time,[81] the bulk of recent data indicates that variation of exposure time over the range 5–240 minutes has remarkably little effect on the injurant action of given dosages of H vapor.[36] Specific experiments to test this point include (1) vapor train experiments with bare skin exposed to H vapor for 3, 10, and 60 minutes;[15] (2) man-chamber tests with H vapor on unclothed skin areas of observers exposed for 15, 30, and 60 minutes both at 90 F and 65 per cent relative humidity and at 78 F and 54 per cent relative humidity;[76] (3) man-chamber tests with H vapor on unclothed skin areas of observers exposed for 30 and 100 minutes at 90 F and 85 per cent relative humidity;[73a] and (4) man-chamber tests of H vapor on clothed subjects exposed for 10 and 240 minutes.[121]

Deviations from Haber's law may be expected when clothed subjects are exposed for short times, because of the effects of clothing in delaying the entrance of H to the skin and/or of effectively prolonging the exposure time by trapping vapor subsequent to the nominal end of the exposure. Deviations may also be expected for short exposure times when the subjects enter a chamber maintained at a temperature and humidity significantly different from those to which they are exposed before the exposure.[73b,91]

Little information is available with regard to the effectiveness of H vapor at very long exposure times or with regard to the effects of repeated small dosages. It appears that the injury resulting from a given total dosage becomes progressively less severe as the dosage is given in more numerous parts and at progressively greater intervals.[142] Observers exposed to a dosage of about 300 mg min m^3 divided in four exposures at 2- or 4-day intervals sustained about the same degree of injury as observers exposed to 100 mg min m^3 in one exposure, and significantly less injury than subjects exposed to a dosage of 270 mg min m^3 in two exposures separated by only 1 day.

Additives and Diluents

The skin-injurant potency of mixtures of vesicants has been tested for a variety of reasons, i.e., because the mixture happened to be produced by manufacturing processes, because it possessed more desirable physical properties (such as low freezing point) than the individual compounds, or because it was hoped that a potentiation of the actions of the components might occur. In general, mixtures of sulfur and nitrogen mustards with each other or with arsenicals, when applied to the skin as small amounts of liquid with evaporation permitted, possess vesicant potencies intermediate between those of the individual components.[14,32,35k,n,o] HQ and HT mixtures are notably more potent than H itself because of the high potencies of Q and T (see Chapter 5).

New vesicants have often been evaluated as dilute solutions in inert solvents, and the relative sensitivities of individuals to H are routinely determined by applications of dilute solutions. It is therefore of interest to note that the injurant action of H at a dose of 65 μg was found to be less when applied diluted in certain solvents than when applied undiluted, and that different results were obtained with different solvents[32] (see Table 18).

On the other hand, in the course of attempts to increase the potency of H by use of additives, one special set of circumstances has been found in which diluted H is more potent than undiluted H.[13] When relatively large doses of H in methyl Cellosolve are

TABLE 18. Effect of solvents on the injurant action of H.[22]

In each instance 65 μg of H was applied, either undiluted or in solution as indicated, to the forearms of human subjects.

T = 67 F, relative humidity = 62%.

Solution delivered	Volume delivered (mm³)	Erythemas No.	Erythemas Size (mm)	Blisters No.	Blisters Size (mm)
100%; H	0.05	18/18	7	12/18	6
50%; H in DPE*	0.10	17/18	7	0/18	..
100%; H	0.05	17/17	7	13/17	5
50%; H in dioxane	0.10	17/17	6	7/17	5
100%; H	0.05	19/19	8	14/19	5
25%; H in DPE*	0.20	9/19	5	1/19	4
100%; H	0.05	19/19	8	14/19	5
25%; H in dioxane	0.20	18/19	7	2/19	5

* Diphenyl ether.

applied to circumscribed areas of pig skin and decontaminated after 5 minutes, certain dilutions (i.e., 1:9 and 1:4) produce as serious injury as the same volume of undiluted H, and other dilutions (i.e., 2:8 to 3:7) produce more serious injury than undiluted H. These observations have been confirmed [23] but it has been demonstrated that the conditions under which the mixture is the more potent are very limited.[23,32,35] In pigs there is no difference between the injuries produced by neat H and diluted H if the exposures are for 10 minutes instead of 5.[23] In man and the pig, neat H in both large and small doses produced much more severe injuries than corresponding volumes of the mixture if decontamination was not practiced.[23,32] If free spread on the skin is permitted and decontamination practiced at 5 minutes, H Cellosolve produces larger but less severe lesions.[23] It is obvious that the use of H Cellosolve mixtures would have no practical use in warfare but the interpretation of the enhanced effect under the special conditions would be of considerable physiological interest.

Detergents notably increase the solubility and rate of solution of H in water [2] and greatly decrease the interfacial tension between H and water.[17,71] It might therefore be expected that addition of wetting agents to H would increase its vesicant effects, particularly on sweating skin. Although a preliminary set of experiments indicated that this was the case,[57] extensive tests with small and large doses of liquid H applied to animal skin and to sweating and nonsweating human skin fail to reveal any potentiation by any of a large number of wetting agents.[23,32,35a,b,k,730] A similar absence of potentiation of vesicancy by addition of wetting agents has been noted in experiments* with HN3.[301]

The desirability of using thickened (viscous) vesicants in warfare has prompted tests of the relative vesicancies of unthickened and variously thickened H and HT mixtures on bare skin and through clothing.[35b,j,k,o,730,119,120] Under a variety of conditions the addition of thickening agents has proved to have remarkably little effect, although small but significant differences have been found in some circumstances [35o,119] and may perhaps be correlated with viscosity.[120]

Environmental Temperature

Numerous observations demonstrate that H as liquid and vapor produces more severe burns at high environmental temperatures than at low temperatures when other environmental variables are maintained unchanged.[12,14,66,76,81,122,134] Pertinent man-chamber and field test data have been summarized and reviewed.[85] The most pronounced effect of temperature change occurs in the range that results in change of skin condition from relatively dry to wet with sweat.[81]

Humidity

Increase in relative (or absolute) humidity in the absence of change of temperature or other environmental variables also increases the susceptibility of the skin to H.[12,31,66,76,81] The effect of humidity change may not be detected when it does not result in much alteration of the moistness of the skin,[81,134] but it is pronounced when it results in marked changes in skin wetness.[81]

Exercise

Exercise which results in sweating during exposure produces a pronounced increase in skin sensitivity to H and the nitrogen mustards.[32,35m,n,135,138,143] Pertinent man-chamber and field test data have been summarized and reviewed.[85]

Wind Velocity — Airflow

Wind velocity assumes great importance in the case of vesicants dispersed as aerosols or fine particulates (see Chapter 15). It seems to be of only minor importance in the case of vapors,[35b,c,d,73,138] and prob-

* An isolated unpublished observation of the reviewer suggests that HN1 vapor may produce more severe injury on skin wetted by water containing a wetting agent (Zephiran – a mixture of high molecular alkyl-dimethyl-benzyl ammonium chlorides) than on skin wetted by water alone.

ably acts principally via its effect on the degree to which the skin is wet with sweat.[40]

Of interest in connection with laboratory studies is the observation that thermal convection currents over the surface of a quiescent animal contaminated with liquid H carry vapor in the direction of flow and result in finger-like extensions of the burned area.[37]

"Radiator Effect"

Exposures of subjects to a given dosage of H vapor in a man-chamber at 90 F and 65 per cent relative humidity produced significantly more severe injury to their arms than exposure of the arms alone of subjects in an arm-chamber at 90 F and 65 per cent relative humidity when the remainder of the body was in a room at 70–80 F and 20–30 per cent relative humidity. When the room temperature was also raised to 90 F and 65 per cent relative humidity, the arm lesions approximated in severity those obtained in the man-chamber. It was concluded that the rest of the body "is capable of functioning as a 'radiator' and thus succeeds in altering the reactivity of the exposed surfaces and reduced the severity of the reaction" when the body is at the lower room temperature.[78] It appears that the "radiator effect" can be interpreted as follows: [81] At a room temperature of 90 F generalized sweating occurs, whereas at 70–80 F it does not (or is mild); thus the exposed forearms were probably sweating in the former case but not in the latter.

Size of Exposed Area of Skin

It has frequently been noted with surprise that the blistering dosage of H or nitrogen mustard vapor as determined by exposure of small areas of skin by vapor-train or vapor-cup techniques is much higher than the casualty-producing dosages of the vapors as determined in man-chamber tests. To a considerable degree, the discrepancy is based merely on differences in the severity of injury taken as an end point, on differences in the sensitivity of the parts of the body surface exposed, on differences in temperature and humidity, and on the radiator effect described above. It is possible that, in addition, exposure of a small area of skin leads to less severe injury per unit area than exposure of a large area of skin. A priori reasoning leads to the conclusion that such must be the case, but no tests have been made to determine the ranges of area in which the postulated effect is and is not of significance.

An interesting unconfirmed observation was that exposure of a narrow annulus of forearm skin to H smoke or vapor at a given dosage resulted in more severe injury if a second annulus 1 or 2 inches distal on the arm had also been exposed than if it had not.[35a]

Clothing

For the sake of completeness it may be mentioned that in general the effects of vesicants through clothing are of greater practical interest than their effects on bare skin, and that assessments of the casualty-producing effectiveness of agents as liquids or as vapors are ordinarily made for troops dressed in either ordinary battle dress or in protective clothing (see Chapters 5 and 6).

23.7.2 Factors of Primary Importance in Determining Susceptibility

Numerous observations demonstrate that human skin that is hot and sweaty is much more susceptible to injury by the sulfur and nitrogen mustards than comparable areas of skin that are relatively cool and dry.[15,32,33a,n.o.p.76,80–82,84,85,122,124,135,138,143,144,145,157,161] In fact, for practical purposes it is considered that sensitivity to vapor of troops not equipped with protective clothing is determined principally by the degree to which their skin is wet with sweat.[85] In all probability skin moisture content underlies the effects of environmental temperature, environmental humidity, exercise and airflow, the "radiator effect," and, in large part, the strikingly different sensitivities of the various parts of the body under cool and temperate conditions.[†] Although it is true that work correlating susceptibility to H vapor with factors which influence sweating and skin wetness has for the most part been rather qualitative, possibilities for a more rigorous evaluation are suggested by a recent Australian study [41] in which account is taken of recently accumulated quantitative data on the cutaneous responses and characteristics of subjects under various conditions with respect to meteorology, clothing, exercise, and acclimatization.[108,109,163]

Particularly illuminating experiments with regard to the effect of humidity and temperature on sweating and sensitivity to H have been performed in the man-chamber at the United States Naval Research Laboratory.[81] Sweating, as measured by a clinical

[†] If acclimatization to hot or cold environments should prove to influence sensitivity to vesicants, possible correlations with the effects of acclimatization on the sweating process and cutaneous heat loss in general should be borne in mind.

starch-iodine test, was determined under the same conditions as susceptibility to injury by H vapor. At 70 F and 62 per cent relative humidity, subjects exposed to H vapor at a dosage of 400 mg min m³ developed intense erythema of only the axillae and showed minimal effects on other parts of the body (protective shorts were worn). Correspondingly, sweat tests revealed active sweating only in the axillae and genital regions. At 90 F and 65 per cent relative humidity, men exposed to 300 mg min m³ showed intense generalized erythema in spite of the lower dosage and, correspondingly, generalized active sweating could be demonstrated. Tests to reveal the effects of relative humidity were carried out at 85 F inasmuch as this temperature is approximately that above which resting men begin to show generalized active sweating. At 36 per cent relative humidity, active sweating was confined to the axillae and genital regions, while at 75 per cent there was moderate generalized sweating. Correspondingly, the injuries produced by exposure to 300 mg min m³ of H vapor were at the low humidity similar to those described above for 70 F, and at the high humidity were similar to those described for 90 F.

That individual variations in sensitivity may in part be related to skin moisture is revealed by the finding that in a man-chamber test a subject who was perceptibly sweating experienced more severe injury than simultaneously exposed subjects who were not perceptibly sweating.[73b] Also in accordance with the concept that skin moisture is important in determining sensitivity is the observation that skin resistance measurements are of some value, probably of more value than skin temperature measurements, in determining which of a group of men will exhibit greatest sensitivity upon exposure to vesicants.[23a,77a] Measurement of skin resistance should help make future work more quantitative.

The following findings demonstrate that the increased sensitivity of hot, sweating skin is due, at least in large part, merely to the presence of water on and in the superficial layers, irrespective of other components of sweat, active sweating, elevated skin temperature, or peripheral vasodilatation:

1. In subjects who are not perceptibly sweating, the vapors of both H and HN1 produce markedly more severe injury on areas of skin that are wet with distilled water or artificial sweat than on comparable areas of skin not wet with water.[30,91,157,161,165]

2. In one experiment no marked difference existed between the severity of injuries produced by exposure to H vapor of (a) skin wet with distilled water and (b) skin wet with 4 per cent sodium chloride.[30]

3. Applications of simulated sebum (lanolin hydrated 50 per cent) to both sweating and nonsweating skin neither increased nor decreased the injury produced by exposure to H vapor.[91]

With regard to the reason the vapors of H and HN1 produce more severe injuries on water-wetted than on dry skin, possible explanations have been discussed[30] but do not appear to have been resolved experimentally.

Other factors than skin moisture are also undoubtedly of importance as primary determinants of susceptibility to injury. The palm, for example, was found to be more resistant than the body surface as a whole even under conditions when active sweating occurred on the palm but not on the general body surface.[91] It is tempting to speculate that the thick horny layer of the palmar skin conferred resistance which more than counteracted the sensitivity that was presumably associated with moistness.

The importance of skin temperature per se cannot adequately be assessed at the present time but it also may play a role of some importance. In the case of extreme cooling, as in the ice-pack experiments described in Section 23.3, it is of importance if for no other reason than because it slows the rate of activation of H and reduces the fraction of penetrated H that is fixed in the skin. Within more moderate and usual ranges of temperatures, there is little effect of temperature on per cent of penetrated H that is fixed in the skin, but the penetration rate of liquid H in both man and animals is markedly affected by the temperature in the skin and or at the skin surface. (see Section 23.3.1). The extent to which this temperature dependence is mediated via an effect on skin moisture content is not known. Other, more direct effects (i.e., effect on rate of penetration independent of skin moisture) may be of equal or greater importance.

23.8 PREVENTION AND MITIGATION OF CUTANEOUS INJURY

A major incentive for many of the studies reviewed in the preceding sections was the hope that they would lead logically to successful methods for mitigating cutaneous injuries due to the sulfur and nitrogen mustards, particularly H. As has been stated, and in contrast with the outcome of studies on arsenicals (Chapters 7 and 31), no conspicuous success has been

achieved except in the development of protective clothing and ointments which act by preventing vesicants from reaching the skin and by destroying liquid vesicant on the skin surface. However, the mechanism studies together with numerous and extensive investigations on decontamination and treatment of H burns have been of value in that they have exhausted many possible avenues of approach and have done much to define and clarify the problems that have not been solved.

It is important to distinguish clearly between the various ways in which beneficial effects might be attained by procedures designed to combat vesicant injury. Considerable confusion existed during the early part of World War II. More recently, several useful definitions have been evolved[21,43,49] and should be presented at the outset:

Protection. The beneficial effects exerted by clothing, ointments, and other physical and or chemical agents employed *before* exposure to a vesicant. A beneficial action can be effected by preventing a vesicant from reaching and entering the skin, or by prophylactic administration of substances designed to have the possible effects of agents used in early treatment.

Decontamination. Any process by which vesicant already on the skin is removed and or inactivated. Decontamination may be effected by mechanical means (e.g., blotting or wiping), by solvent or detergent action, or by chemical reaction of the vesicant with a decontaminating agent. Destruction within the skin of *penetrated* free vesicant not removed by surface decontamination is considered early treatment.

Treatment. Something other than protection or decontamination; something done to obtain a beneficial action *after* the vesicant has penetrated the surface of the skin. Treatment may be local, as discussed in this section, or general (see Chapter 22). It may be early (specific) or late (nonspecific, definitive). *Early* treatment refers to the administration of substances to obtain therapeutic effects (1) by reaction in the tissues with free vesicant or its injurious products, (2) by removal of fixed vesicant from tissue components, or (3) by exerting an action on tissues which enables them to ward off or overcome the effects of a vesicant or its products. Thus, early treatment implies a procedure aimed specifically at inhibition of the action of the vesicant or its products, either by altering them in such a manner that they cannot injure the cells or by altering the cells in such a manner that they protect themselves. *Late treatment* refers to the use of substances and or procedures to obtain beneficial effects on established lesions (e.g., by accelerating healing).

23.8.1 Protection

By far the most effective method of combatting the skin-injurant effects of H and the nitrogen mustards is to prevent the vesicant from reaching the skin. Work to achieve this end is reviewed elsewhere. In brief, impervious clothing affords excellent protection even against gross liquid contamination but imposes such severe limitations on the efficiency of the wearer that its practical use is restricted to special tasks.[38] Notable progress has been made during World War II in the development, evaluation, and production of permeable protective clothing. (See Chapters 5, 6, 26-30.) Progress has also been made in the development of ointments which can be used for protective purposes (see Chapter 25).[10,48] The difficulties imposed by the irritancy of the earlier ointments have in large part been overcome. However, the prophylactic value of thin films of ointment against liquid H is small, and against H vapor it is limited by the tendency of the ointment to become rubbed or washed off the skin.

Only limited attempts have been made to achieve protection by augmenting the resistance of the skin itself to penetration and injury or by prophylactic administration of materials designed to detoxify H and other related agents within the skin. At the present time these approaches appear to hold little promise.

As described in Chapter 22, the systemic effects of H and nitrogen mustards entering the body through the skin can be alleviated to some extent by parenteral administration, *shortly* before contamination, of relatively *large* amounts of certain substances with high competition factors (e.g., sodium thiosulfate, hexamethylenetetramine, or sodium monoethanedithiophosphonate). However, this type of systemic prophylaxis has not been found to exert a beneficial action on the local skin lesions at the site of application of the vesicant.[7,38] It cannot be considered of practical value even as a means of protecting against systemic effects because of the limited degree of protection attained, the large doses of protective agent required, and the brief period during which protection is achieved (see Chapter 22).

A few preliminary experiments have been performed to test the possible protective effects of

intradermal administration of various materials. In one investigation [37] sodium chloride was used because of the retarding action of chloride ion on the rate of activation of H (see Chapter 20), thiosulfate because of its high competition factor (see Chapters 19 and 20), and leach "spreading factor" [38] because of its presumed facilitating action on the movement of these substances through the intercellular spaces. In rabbits, injection of 1.8 per cent sodium chloride, either with or without addition of spreading factor, shortly before application of 1 mg of H to the injected site had no effect on the severity of the lesion that developed. Injection of 5 per cent sodium thiosulfate without added spreading factor had a slight beneficial effect, and with spreading factor a definite beneficial effect. Spreading factor alone was not tested. The favorable result obtained with thiosulfate seems to confirm the obvious prediction that beneficial results could be obtained *if* one could maintain in the skin sufficiently high concentrations of an innocuous substance which competes for or otherwise destroys or detoxifies H or the nitrogen mustards.

23.8.2 Decontamination

When a liquid sulfur or nitrogen mustard is placed on the skin, penetration and the initial apparently irreversible injury-producing steps occur rapidly (see Section 23.3). In the case of H, severe local injury can be avoided only if the liquid is effectively removed or destroyed within at most a few minutes. Inasmuch as penetration rate is augmented by increase of environmental and or skin temperature (see Section 23.3.1), the time factor is more critical at high than at low or moderate temperatures. The importance of these time and temperature factors is revealed by the data presented in Sections 23.3.1 and 23.3.2 and is further illustrated, for applications of small doses of H, by the data of Tables 19 and 20. Studies with animals have also been made.[36]

Although small doses of liquid H disappear from the skin surface within a matter of minutes, large splashes may not completely disappear by evaporation and penetration in less than several hours (see Section 23.3.1). Delayed decontamination can be expected to be of value so long as liquid is present. It cannot prevent a very severe local lesion, but it may reduce the size and depth of injury and it can eliminate the possibility of further spread of vapor and liquid to other parts of the body.

Of the possible methods of effecting decontamination, mechanical removal (e.g., by blotting or wiping) is to be recommended for the removal of the bulk of large splashes of vesicant. It is not, however, so effective as other means of removing all the vesicant that is on or in the superficial layers of the skin [21,24] (see also Table 21 and Section 23.3.1).

For thorough surface decontamination of all liquid vesicant, use of solvents in large amounts and use of a substance which reacts chemically with the vesicant to detoxify it are highly, and approximately equally, effective.[12,21,24] For experimental purposes it is often convenient to use a solvent (e.g., petroleum ether or pentane for H decontamination). The solvent must be used freely and with care, however, if the vesicant is not merely to be spread on the skin and the lesion consequently enlarged. For use in the field, chemical decontamination has several advantages [24] and is the method which has been adopted for standard use.

TABLE 19. The time factor in decontamination of liquid H.[24]

The H was applied by No. 3 Edgewood rod (i.e., ca. 32 μg dose) to the forearms of human subjects. The sites were decontaminated after the stated intervals by application of a chloramide-containing ointment. T = 66 F.

Note that decontamination at 3 minutes was of marked value but, with the small dose of H employed, decontamination at 6 and 9 minutes was ineffective in spite of the relatively low environmental temperature.

Interval between contamination and decontamination (min)	Number of men	Erythemas Per cent	Erythemas Avg size (mm)	Blisters Per cent	Blisters Avg size (mm)
3	333	10	6	8	3
6	32	100	6	81	4
9	38	98	6	82	4
Untreated control	55	100	6	78	3

TABLE 20. Effect of temperature on the effectiveness of decontamination of liquid H 10 minutes after its application.[24]

65-μg doses of liquid H were applied to the forearms of human subjects. Ten minutes later decontamination was carried out with a chloramide-containing ointment.

Month	Temp (F)	Relative humidity (%)	No. of men	Untreated control % blisters	Untreated control Size (mm)	Decontaminated % blisters	Decontaminated Size (mm)
March	60	40	23	80	8	52	5
	65	41	20	90	5	50	5
June	76	47	13	80	7	73	7
	80	61	62	98	6	10	6

TABLE 21. Comparison of chemical and mechanical decontamination of liquid H.[21]

60-μg doses of liquid H were applied to the forearms of human subjects. Chemical decontamination was effected by use of a chloramide-containing ointment, mechanical decontamination by wiping with cleaning tissue.

T = 60 F, relative humidity = 65%

Interval between contamination and decontamination (min)	Method of decontamination	Blisters Number	Blisters Avg size (mm)
	Chemical	0/9	..
	Mechanical	3/9	5
3	Chemical	3/10	5
	Mechanical	8/10	4
5	Chemical	4/10	5
	Mechanical	8/10	5

Numerous substances of various types have been tested[7,9-11,20,21,23,24,40b,63d,e,f,o,p,64,66,71a,97,99,113b,c,134] as chemical decontaminants for H. They have included various oxidizing agents and substances that in aqueous solutions have high competition factors (see Chapters 19 and 20) for H. Some of them are as effective as the chloramides described in Chapter 24. However, none has been found that is superior to these compounds or more convenient to use.

The nitrogen mustards are not readily oxidized by the chloramides that are currently in most common use as decontaminants for H. However, other chloramides which do effectively decontaminate the nitrogen mustards by chemical reaction have become available (see Chapters 6 and 24). Oxidizing agents such as potassium permanganate are also effective. For experimental purposes it is sometimes convenient to apply dilute acids. The relatively insoluble amines are then converted to their corresponding hydrochlorides, which are highly soluble and can conveniently be washed away.

In the testing of chemical decontaminants it is important to use large amounts of vesicant.[24] Small amounts may be so effectively diluted by the solvent or vehicle in which even an ineffective decontaminant is applied that no injury develops. When the same ineffective decontaminant is tested against a large dose of vesicant, the latter is merely spread and a severe, widespread lesion develops. This circumstance explains the finding that small doses of HN3 could effectively be decontaminated by M-5 ointment, the chloramide of which does not readily destroy HN3;[72b] the ointment base alone was as effective as the ointment containing the chloramide.

In the case of exposures to vapor there is so little free vesicant on or in the superficial layers of the skin and accessible to "surface" decontaminants that decontamination can be of little value from the practical standpoint (see Section 23.3.2).[10,21,71b] A recently obtained set of data relating to this point is presented in Table 22. The data do not suffice to differentiate between the possibilities that decontamination was of no value or of slight value. Experiments indicating that surface decontamination can be of slight value are presented in Section 23.3.2.

TABLE 22. Attempted decontamination of H vapor burns.[10]

Vapor cups were applied for 6 minutes and decontamination effected by application of a chloramide-containing ointment.

T = 69 F, relative humidity = 18%

Interval between contamination and decontamination (min)	Erythemas Number	Erythemas Avg size (mm)	Blisters Number	Blisters Avg size (mm)
0	13/13	9	3/13	5
Untreated control	12/13	9	3/13	8
5	15/15	8	1/15	3
Untreated control	15/15	9	3/15	6

23.3.3 Early Treatment

No agent or procedure of significant value in the early treatment of H or nitrogen mustard burns of human skin has yet been discovered in spite of extensive researches.[7,9-11,21,22,23,38a,b,c,113b,d,e] It will be apparent that the value of a procedure for early treatment can be properly assessed only when the possibility is obviated that it merely effects surface decontamination. Thus, in case of liquid burns, surface decontamination must first be performed or the treatment delayed until all the applied agent has either evaporated or penetrated the skin. It would seem that vapor burns might more conveniently be used in the evaluation of early treatments.

The amount of free H that is not removed from human skin by surface decontamination is so small and its persistence time so short that treatments based on its destruction in the skin cannot be expected to be of significant value (see Section 23.3.2). For instance, 2 minutes after surface decontamination of human skin contaminated with liquid H there

is in the skin only in the order of 1 μg of free H per square centimeter. If 12 per cent of this (i.e., 0.12 μg cm²) were to become fixed,[12] it would correspond to only the threshold value for mildest injury, or to the amount fixed per minute of exposure to liquid H at an environmental temperature of ca. 75 F.[12] In pig and rabbit skin the reservoir of free H is larger and it persists longer (see Section 23.3.2). Thus in these species early treatment based on its removal or inactivation might be of greater value. This difference between human and animal skin must be borne in mind when treatment procedures are tested in animals.

It is not known to what extent "surface" decontamination removes liquid vesicant that has penetrated into the superficial layers of the skin. Some studies suggest that diffusion in and out of the more superficial (dead) layers is relatively free but that a barrier to the passage of solutes exists at the transitional layers between cornified and noncornified epithelium.[102] Histochemical evidence has been adduced that the chloramides of antigas ointments penetrate into the skin but no detectable amounts of available ("free") chlorine could be found in skin inuncted with these ointments.[103] It has been demonstrated that various substances penetrate the skin more effectively from mixtures of ethyleneglycolmonoethylether (Cellosolve) with diethyl ether than from aqueous solutions.[28] Thus the use of carriers to promote the penetration of therapeutic agents might prove to be of value.

There is no evidence that any of the many tested procedures of treatment effectively remove fixed H from tissue components in living skin in the manner that BAL removes trivalent arsenic. The one apparent exception to this statement was discussed in Section 23.3.3. The bulk of the chemical evidence (see Chapters 19 and 21) gives little hope that removal can be effected by procedures which in themselves would not be highly injurious, although some leads which may merit further investigation have become available.[11b,f,l,t,u] It has often been assumed on the basis of analogy with the effects of BAL in arsenical poisoning that the problem of combatting H injuries would in large part be solved *if* one could discover a procedure which removes fixed H from the skin and which is not in itself injurious. This would not necessarily be the case. Unlike the arsenicals, H reacts not only with sulfhydryl groups but also with various other side-chain groups in tissues (see Chapters 19 and 21). One cannot be assured in advance that the skin proteins would be regenerated in native form upon removal of the fixed H, or that the cell machinery would not be permanently disrupted as a consequence of even brief combination of some of these groups with the vesicant.

Nor do there appear to be favorable clues suggesting a method of treatment based on exerting an action on tissues which would enable them to ward off or overcome the effects of H or its products.

A report[11b] that vesication may be prevented by prompt and prolonged applications of BAL to skin that has been burned with H led to some hope that a useful procedure for treating H injuries had been found. Although the finding has been amply confirmed,[28,63k,l] it is not believed to offer a procedure of practical value.[28] Vesication is prevented not because injury is reversed or lessened but because the character of the pathological response is altered. Although BAL appears to reverse the inhibition of anaerobic glycolysis produced by application of H to skin,[28] the action of BAL on vesication is not specific for H. It also inhibits the formation of blisters due to cold,[78] although not the more rapidly forming ones due to heat or tincture of cantharides.[28,63m]

Caustics (e.g., trichloroacetic acid) can also be used to prevent vesication due to H, HN2, HN3, or L. They, too, act not by alleviating injury but by adding insult to injury and thereby altering the gross manifestations of injury.[28,98]

The circulation in H lesions is active for many hours after erythema has appeared and the capillary walls are abnormally permeable, permitting even large molecules to accumulate in the tissue spaces of the skin. Consequently, if a substance of value in early or late treatment could be discovered, the conditions for its administration via the blood stream would appear to be favorable.[27]

23.3.4 Late Treatment

The treatment of definitive (established) vesicant injuries falls outside the scope of this chapter. In brief, it seems to present no fundamental features not encountered in other kinds of burns. Some treatments are more favorable than others but no means of *markedly* accelerating the healing rate have been discovered,[4b,13a,i,m,o,v,z,34,67,72d,i,z,90,94,101,119,124,127] except that, as in thermal burns,[41,43bb,dd,ff,gg,hh] promotion of slough removal by prolonged applications of weak acids (i.e., pyruvic acid) in starch paste or other vehicles[4b,i,o,w,x,y,z,ee,ff,gg,72f] appears to be of some value.

23.8.5 Methods of Evaluating Procedures for Protection, Decontamination, and Treatment

Experience that has been gained during World War II has been summarized in detail in a report [24] that should be consulted in the original if further studies on the decontamination and treatment of skin exposed to sulfur or nitrogen mustards should be contemplated. The methods that have been developed for evaluating ointments designed for protection and decontamination have also been authoritatively reviewed.[48,49]

PART IV

PROTECTION AGAINST CHEMICAL WARFARE AGENTS

Chapter 24

CHLORAMIDES FOR PROTECTION AGAINST VESICANTS

By Homer Adkins and Wilkins Reeve

24.1 INTRODUCTION

Compounds carrying a positive chlorine atom on nitrogen have proved to be the most effective agents for detoxifying the vapors of H [*bis*(β-chloroethyl) sulfide] impinging on skin or fabrics.[9,12,13] A great many representatives of this type have been prepared in searching for the most satisfactory compound to meet a variety of requirements.[5,17,28,29,31,34,35]

First, the low concentration of the chloramide on the skin or in clothing must react very rapidly on contact with H vapor at very low concentrations of a few micrograms per liter.[1,2,7] Second, the compound and its hydrolysis and reaction products must be of such physical and chemical characteristics as will permit it to retain its capacity for reacting with H for long periods of time after it has been impregnated into clothing. Third, the compound must be stable in storage, and also when impregnated in fabrics or incorporated in an ointment. Fourth, a chloramide for use on clothing should not be reactive toward fabrics of cotton, wool, or synthetic fiber, and so reduce their tensile strength under the various conditions of temperature, humidity, perspiration, dirt, and laundering to which fabrics are normally subjected. Fifth, the compound should be as little irritating as possible to human skin, since it may be worn for days in the case of an ointment, and for weeks and months in the case of impregnated clothing.

In addition to these various requirements with respect to use, no compound can be considered unless it can be produced from available materials by a practical and economic process suitable for large-scale operation. Even for use in an ointment, it was considered necessary to make provision for the production of millions of pounds of material. For reasons of economy in production and transport, it is desirable that the concentration of the effective part of the compound, i.e., the positive chlorine, constitute as large a portion as possible of the total weight of the compound.

No known compound completely and satisfactorily meets all of the requirements enumerated above. However, CC-2 for clothing and S-330 for protective ointments appear at this time to be, by all odds, the best and most useful compounds for protection against H. CC-2 has the disadvantage that only 14.5 per cent of the total weight of the pure compound is effective for the detoxification of H. The process for producing it is relatively expensive, and the requirements in material and equipment are rather heavy. Nevertheless, its high and sustained activity against H, its relative nonirritancy, and its relative inactivity against fabrics make it the most satisfactory known impregnite for clothing.[32,36]

S-330 carries more than twice as much active chlorine per unit weight as does CC-2, and it is obtainable by a somewhat simpler and more economic process from the standpoint of both materials and equipment.[17,23] It is less irritating to human skin than is CC-2,[12] and, without the addition of stabilizers, it produces less tendering of a fabric than does CC-2.[27] However, S-330 apparently does not retain its activity toward H when impregnated on a fabric, so that it is unsatisfactory for use in protective clothing.[27]

CC-2 and S-330 react more sluggishly with the nitrogen mustards than with H, with the result that their usefulness in protecting against these agents is limited. Certain compounds are known and are referred to below, which are effective against the nitrogen mustards, as well as against H. However, these more reactive compounds are much more irritating to the human skin than are CC-2 or S-330, and so cannot long be tolerated in an ointment or in clothing.

Perhaps little need be added to these statements regarding the merits of CC-2, S-330, and the other known chloramides. However, the following sections summarize the changing conditions and new discoveries which have, during the period of the recent war, brought about changes in the requirements and availability of chloramides.

24.2 DEVELOPMENT AND COMPARISON OF CHLORAMIDES

The situation in 1941 and in 1942 was critical with respect to availability of impregnites for protective clothing. The British had determined to use Impreg-

nite E,[18] but this compound was not considered satisfactory by the United States Chemical Warfare Service [CWS] representatives. All later work has shown that Impregnite E is inferior in every way to CC-2,[20,21] which was discovered and developed at Edgewood Arsenal. However, the situation in regard to the production of adequate quantities of CC-2 was quite unsatisfactory until 1943.[22] CC-2 was produced in a small plant in Edgewood Arsenal by a process which gave a product of variable quality. In fact, when the material manufactured by the diphenylurea (DPU) process at Edgewood was sold to the Navy, it was the cause of excessive deterioration of fabrics, and gave it in 1942 an undeservedly bad reputation, especially with the representatives of the Navy.

The newer trichloroaniline (TCA) process for making CC-2 [20] had not been adequately developed in the laboratory before it was necessary to put it into production on a large scale. When the CWS plants were put into operation, the production of the material was far below the requirements and the rated capacities of the four plants. Attempts to increase production naturally resulted in a decrease in quality of material, so that some of the CC-2 produced by the TCA process in 1942 was no better than that produced by the older DPU process.

The process for producing CC-2 is singularly unattractive because of the materials required, and because of the corrosive character of the various reaction mixtures and by-products.[22] Only one-eighth of the chlorine used in the manufacture — even if the yields were 100 per cent — would occur in the product in a form which is active against H. A very large amount of acetic acid is required as a solvent, and, during 1942, about 4 pounds were lost per pound of CC-2 produced. Great difficulty was encountered because of the corrosion caused by mixtures of hydrogen chloride and acetic acid, so that the construction and maintenance costs in the plants were excessive. Moreover, the amount of acetic acid necessary for the production of the required CC-2 was apparently in excess of that available in this country. Benzene is a necessary starting material for CC-2, and this was also in short supply in this country in 1942. For these various reasons, it seemed incumbent upon representatives of NDRC to attempt to develop economical processes for producing a fabric impregnite not possessing these disadvantages of production.

The surveys made in the Naval Research Laboratory [23] and elsewhere [4] had uncovered nothing so attractive as S-461 or S-328 as possible impregnites. The representatives of CWS, in the summer of 1942, were much more favorably inclined towards S-328 than towards S-461, because the former is somewhat soluble in tetrachloroethane and so could be used in the CWS solvent process for impregnation of fabrics. S-328 requires toluene as a starting material, which is converted successively to benzaldehyde, benzoin, benzil, diphenylglycoluril, and then chlorinated to S-328. Thus, S-328 suffers one of the disadvantages of CC-2, i.e., it depends upon the availability of an aromatic hydrocarbon. However, because of the interest of representatives of CWS, and in order to provide insurance against possible failure in the development of S-461, the process for producing S-328 was worked out on a pilot-plant scale.[15,24]

On the basis of work at the Naval Research Laboratory, S-461 was believed to be non-irritating and quite reactive with H.[25] It is more stable towards hydrolysis and thermal decomposition than is CC-2 or any other compound reactive with H.[4] However, once thermal decomposition is under way, it is self-propagating. One pound of S-461 contains as much positive chlorine as 3 pounds of CC-2.

S-461 can be produced in almost quantitative yield from diacetyl, which was an attractive intermediate. The representatives of the Naval Research Laboratory had, during the early part of 1942, stimulated a great deal of interest in various companies in the preparation of diacetyl. Therefore, S-461 was prepared from diacetyl,[24] so that a pilot plant process would be available if, as seemed from time to time possible, diacetyl could be produced by fermentation. Unfortunately, diacetyl has never become available through fermentation, although it no doubt could be produced by fermentation of sugar to 2,3-butylene glycol, followed by oxidation.

Since there was, in the opinion of the representatives of the National Defense Research Committee [NDRC], little likelihood that diacetyl would become available, it appeared necessary to obtain S-461 from some other material. Studies were undertaken in December 1941 to develop a process for preparing S-461 base by the nitrosation of methyl ethyl ketone followed by reaction with urea. This development led to a satisfactory process for producing S-461,[3,4,10,11,26] which was used on a manufacturing scale. Still later, a more economical process was worked out in which methyl ethyl ketone is oxidized with air over a catalyst to give a dilute solution of diacetyl, from which S-461 base is prepared by reaction with urea.[10] This process makes S-461 poten-

tially available at a cost of about one-tenth that of CC-2, the comparison being made on the basis of equivalent amounts of chlorine active against H. The chlorination of S-461 base to S-461 is carried out in a slightly alkaline medium, so that there is no difficulty with corrosion.

The chief disadvantage of S-461 as an impregnite, as the matter was understood in 1942, was its tendency to lower the tensile strength of fabrics which were impregnated with it and then stored under simulated tropical conditions. It was felt that the original objection, that S-461 could not be used in the solvent process because of its insolubility, had disappeared with the development of the aqueous process for impregnation (see Chapter 26), and, in fact, S-461 as produced commercially was more simply utilized in the aqueous process than was CC-2.[4] Subsequent work showed that fabrics impregnated with S-461 and a suitable stabilizer were not greatly inferior in storage stability to those impregnated with CC-2 and the preferred stabilizers. All the tests then available indicated that S-461 and CC-2 were approximately equivalent with respect to effectiveness against H, except that S-461 had the advantage that, because of its higher content of active chlorine per unit weight, fabrics could be impregnated to a much higher level of active chlorine per unit area, thus providing a greater capacity for detoxifying H.[1,2,4] This was considered to be particularly important in connection with protection against liquid H spray.

S-328 proved to be quite unsatisfactory as an impregnite; although the agent was active against H in freshly impregnated fabrics, its reactivity in some instances decreased greatly on storage;[36] thus, fabrics which showed a fairly high concentration of chlorine per unit area offered very poor protection against H as judged by laboratory tests. S-461 also had a disadvantage in that a rather vigorous thermal decomposition occurred in the solid material if it was once initiated by sparks or a temperature of the order of 200°C.[19,24] Later work in 1943 showed that fabrics impregnated with S-461 were significantly more irritating than those impregnated with a good grade of CC-2.[33]

Two other compounds, S-210 and S-330, were given serious consideration as impregnites for protection against H.[37] Both the Army and the Navy procured in large quantities a decontaminant (RH-195), reactive with H, which cannot be used as an impregnite. However, the closely related compound, S-210, made from the same materials used in making RH-195 with the addition of formaldehyde, was considered to be an attractive possibility as an impregnite. It now appears that this compound is somewhat like S-328, in that the agent does not retain its activity toward H under all conditions.[20,22]

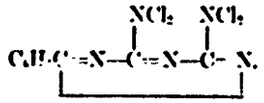
The investigators at the Naval Research Laboratory were greatly interested in utilizing S-330 as an impregnite. S-330 was first prepared at the Naval Research Laboratory by a process similar to that used for S-328, except that guanidine carbonate was used instead of urea for condensation with benzil. Its preparation and use were not desirable for several reasons: Neither benzil nor guanidine carbonate were available in any considerable quantity. Second, the process for producing the compound was a rather laborious one; the product was obtained in low yield and a practical method for separation of the products of the condensation was not known. A sample of S-330 produced by a commercial concern at the request of the Naval Research Laboratory, late in 1942, was quite unsatisfactory with respect to homogeneity and stability. The material available at the end of 1942 was of such poor quality that its use could not be seriously considered. However, small quantities of pure material became available early in 1943 as the result of work done under NDRC contracts[17,21] and also from the Naval Research Laboratory.

During the first eight months of 1943, fairly satisfactory processes for producing and isolating pure S-330 were developed by the Naval Research Laboratory and NDRC, and steps were immediately taken, under the auspices of NDRC, to carry the process for producing S-330 through pilot plant development. The process developed at the Naval Research Laboratory for the preparation of S-330, utilizing benzil and guanidine carbonate, was taken over under an NDRC contract,[23] and, with improvement and simplification, has become the process by which about 2 million pounds of S-330 has been produced under an Army procurement contract for incorporation into the protective ointment M-5. Another and apparently more economical process for producing S-330 has been developed, utilizing guanidine nitrate instead of guanidine carbonate.[17]

Thus, prior to the fall of 1943, S-330 could not be seriously considered as an impregnite because of its unavailability, and by that time it had been established that S-330 was somewhat like S-328 in that it did not, under all conditions, retain its activity

toward H after impregnation on cloth. The advantage of S-330 as an impregnite depended on the fact that it brings about less tendering of the fabric than any other known chloramide. However, CC-2 impregnated fabric containing zinc oxide or calcium carbonate as a stabilizer has no greater ill effect upon the tensile strength of a garment during storage than does S-330 impregnated without a stabilizer. However, S-330 with a stabilizer has probably less effect during storage on the tensile strength of herringbone twill than any known chloramide. Of all known compounds active towards H, S-330 in an ointment is unquestionably the least irritating to the skin. (See Chapter 25.)

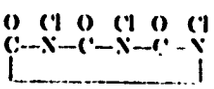
The ineffectiveness of CC-2 toward the nitrogen mustards[5,8] led to a search for a compound as effective against the nitrogen mustards as is CC-2 against H.[18,23] The best compound now known for this use is S-43[8] It is made by the chlorination of 2-phenyl-4,6-diamino-1,3,5-triazine, which is obtained in high yield by the condensation of phenyl cyanide and cyanoguanidine. There are four active chlorines in the molecule of S-436, which may be represented by the formula,



The compound is stable and melts without decomposition at about 138 C. The corresponding compound with three chlorines is called S-366; that with two is known as S-277. The fourth chlorine in S-436 is almost as reactive toward the nitrogen mustards as is CC-2 towards H; the two chlorines in S-277 are no more reactive than those in CC-2. The third chlorine in S-366 is intermediate in its reactivity between the fourth chlorine in S-436 and the two chlorines of S-277.

S-436 is sufficiently stable on a fabric to make it possible to use it in a field or helmet process. The irritancy caused by S-436 on a fabric is apparently similar to that of S-461, so that it might be feasible to use it for protection against the nitrogen mustards. The protective value of S-436 impregnated in a fabric has not as yet been confirmed by tests in a toxic gas chamber.

Improved processes for producing another chloramide, referred to by the Germans as Decontaminant 40, i.e.,



was developed.[27] The new process for preparing Decontaminant 40 utilizes a new method for preparing cyanuric acid, through the reaction of ammonia and phosgene. The process is similar to that developed for the preparation of methyl isocyanate from methylamine and phosgene.[27] Decontaminant 40, like S-436, is quite stable and is very effective for decontamination, particularly for the nitrogen mustards.

Chapter 25

PROTECTIVE OINTMENTS

By *Homer Adkins* and *Wilkins Reeve*

25.1 INTRODUCTION

A SATISFACTORY OINTMENT for protection against mustard gas (H) depends, first, upon obtaining a suitable active agent, and, second, upon devising a vehicle for applying and retaining the active agent on the surface of the skin. It is difficult to obtain a completely satisfactory nonirritating compound which will detoxify H instantly in low concentration and yet will not cause skin irritation under tropical conditions. The problem of obtaining the most suitable active agents has been considered in Chapter 24. No other practical type of compound has as yet been found which is effective as a protective agent against H.[2,4,5,6,9,11,14,27,29] The primary requisites of the active agent are that it be available in adequate quantities, that it be stable on storage in the vehicle and containers selected, and that it not irritate the skin, even though it is applied repeatedly under tropical conditions over a period of many hours or several days. A study of a great many different chloramides has shown that the one made from benzil and guanidine, coded S-330, is the most satisfactory agent from the standpoint of irritation and stability on storage.[7] Experience has shown that it is procurable in almost any desired quantity at a reasonable cost.

The primary requisite in a vehicle is that, in addition to being nonirritating, it retain the active agent on the skin as long as possible. No vehicle so far obtained is completely satisfactory in giving long persistence of protection without interfering with the subject's handling of tools and weapons. It appears, however, that at this time the protective ointment procured by the Army and Navy, and coded M-5 or S-330 protective ointment, is the most satisfactory. Thus the work on protective ointments is, in a certain sense, summarized in the formula for M-5 discussed below.

25.2 DEVELOPMENT AND EVALUATION OF PROTECTIVE OINTMENTS

Prior to December 1940, the Toxicological Research Laboratory of the Chemical Warfare Service [CWS] had developed at Edgewood Arsenal an ointment which they believed was satisfactory for protection and decontamination against H.[11,14] The ointment, designated M-1 and containing 25 parts of dichloramine-T, 65 parts triacetin, and 10 parts cellulose acetate butyrate, was recommended for manufacture at that time. Since dichloramine-T was not immediately available, an ointment containing chloramine-T, designated M-2, and one containing dichloramine-B, designated M-3, were manufactured in small amounts. The designation of M-1 was then changed to M-4. The fact that M-4 was too irritant to be used as a protective ointment was officially admitted in the fall of 1942, and it was thereafter recommended for decontamination only.[15,16]

The British had found ointments containing chloramine-T or dichloramine-T too irritant for use as protective ointments. About the middle of 1941, they produced a protective ointment of the vanishing-cream type composed of 25 parts Impregnite E, 20 parts diethyl phthalate, 10 parts hydrogenated whale oil, 4 parts sodium stearate, 2 parts potassium stearate, and 39 parts water.[24,25] This ointment is known as A.G. No. 5. Because of the unavailability of hydrogenated whale oil, another ointment, known as A.G. No. 6, was recommended for procurement in which hydrogenated peanut oil replaced the whale oil. Difficulties were encountered in the manufacture of A.G. No. 6, so that it was not produced in any considerable amount. Neither A.G. No. 5 nor A.G. No. 6 was acceptable to United States Armed Services because of lack of stability from both the physical and chemical standpoints, although they were recognized as being quite nonirritating, and as being quite satisfactory as a decontaminant for human skin, clothing, and weapons.[11,23]

It was widely recognized in 1942 that the ointments available to the Armed Services were defective in certain fundamental respects. The M-4 ointment of the Army was irritating when applied to the skin and was unstable in storage. It appeared that no ointment containing dichloramine-T (the active agent in M-4) would be satisfactory, either with respect to effect on skin, or stability in storage. The agent in the British ointment was satisfactory from the standpoint of irritancy, but not from the standpoint of availability or acceptability to representatives of the

Armed Services. The water-oil emulsion used as the vehicle in the British ointment was unsatisfactory from the standpoint of stability on storage. It thus seemed necessary to select the most stable and least irritating potentially available chloramide, and to incorporate it into an anhydrous vehicle.

The chemical and physical characteristics of S-461 and S-328 seemed to make them potentially valuable as ingredients for a protective ointment. These compounds had been prepared at the Naval Research Laboratory and found to be stable towards heat and water, and relatively nonirritating. The possibility of using these compounds in a protective ointment was called to the attention of representatives of the Chemical Warfare Service in November 1941. However, a favorable response was not received, perhaps because at that time the representatives of the Chemical Warfare Service believed that the active agent in a protective ointment must be in solution and not merely dispersed. Neither S-461 nor S-328 is sufficiently soluble in any suitable solvent to make it possible to secure an ointment similar to M-4 in which the active agent is in solution in triacetin.

Ointments containing an insoluble chloramide in suspension in a nonaqueous medium had apparently not hitherto been prepared or evaluated. However, a practical solution of the problem of making up such an ointment was obtained in March 1942, within eight days after it was proposed by a representative of the Naval Research Laboratory. The ointment consisted of S-461 (34 per cent) and magnesium stearate (14 per cent), dispersed in liquid triacetin (52 per cent). S-461 was the least irritating available chloramide until S-330 was tested in August, 1943. The magnesium stearate was selected as the second solid component of the ointment, in order to make it more adherent to the skin and to facilitate spreading, and to give it better "cosmetic properties." The ointment so compounded was tested for stability in storage[1] and for protection[22,23] and irritancy. It was adopted by the Navy in August 1942, and procured in September 1942, and again in March 1943. For more than a year and a half the Navy S-461 ointment was the only protective ointment available, although procurement of many millions of tubes of M-4 ointment was continued by the Army until the fall of 1943.

Tests made on the Navy S-461 ointment during the last half of 1942 and the first half of 1943 showed that the ointment caused irritation in a considerable number of those who applied it, three to six times in succession, during a 3-day period.[3,12,13,16] During January, February, and March, 1943, the situation with regard to a protective ointment was considered by an impartial committee at the request of the CWS-NDRC Technical Committee.[10] It was concluded that the S-461 Navy ointment, or a modification carrying a lower concentration of the active agent, was the best protective ointment available at the time. This conclusion was shared by the representatives of the Canadian Army, who, upon the basis of the information available from United States, British, and Canadian sources, proceeded with the procurement of S-461 and the adoption of its use in a protective ointment having the same components as the ointment procured by the United States Navy.[10]

The difficulties in developing a protective ointment were due, in large part, to the lack of adequate means for testing an ointment for protective value under realistic conditions. The only method available for testing the protective value of an ointment was the inadequate Edgewood cup method.[3] Realistic and comparative tests had not been carried out to determine the irritancy caused by repeated application of a protective ointment. Beginning in the spring of 1943, routine testing for irritancy was carried out under a National Defense Research Committee [NDRC] contract, and the leading candidates evaluated more thoroughly under various contracts with the Committee on Medical Research [CMR].[7] The results obtained led to the discovery that S-330 was the least irritating of the known chloramides, with pure CC-2 and S-461 being the second and third candidates, respectively. S-330 is also very stable when compounded into an ointment and stored for several months at 50° C.

During the summer and fall of 1943, tests were carried on in toxic gas chambers at Edgewood Arsenal and at the Naval Research Laboratory, whereby ointments could be given a more realistic evaluation as to their effectiveness for protection under conditions somewhat similar to those encountered in the field.[17] These tests demonstrated what had already been suspected, that the vehicle in which the active agent was dispersed was of more importance in determining the persistence of protection than was the particular active agent, or the amount of it present in the ointment. Methods for the preparation of pure S-330 having been worked out during the first eight months of 1943, it became the active agent preferred for use in a protective ointment. Renewed attention

was then given to the question of the most suitable vehicle for S-330.

In order to secure a better adherence to the skin during exercise, it proved advantageous to incorporate cellulose butyrate acetate into the ointment.[17] The addition of titanium oxide was also found to be advantageous, because its use eliminated some of the difficulties incidental to the manufacture of an ointment containing cellulose acetate, and it also improved the spreading qualities. It seemed advisable to incorporate dyes into the ointment for the sake of camouflage.[8] The formulation of the M-5 ointment adopted in December 1943 was 25 per cent S-330, 4 per cent cellulose acetate butyrate, 9 per cent titanium dioxide, 9 per cent magnesium stearate, 52 per cent triacetin, 0.8 per cent sulfanthrene brown G, and 0.2 per cent monastral fast green G. An ointment of approximately this composition appears to be the most satisfactory yet attained for protection against H and for decontamination of the skin.[18,20, 21,28,35,37,38]

If S-330 is not available, CC-2 of good quality is probably the preferred active agent for use in a protective ointment.[3,7] The possibility of using CC-2 in an ointment was discarded by the representatives of CWS for reasons that now do not seem to be applicable.[9] Until the middle of 1943, consideration could not be given to the use of CC-2 in a protective ointment, because of its unavailability for this purpose. The quality of CC-2 available in 1942 was such that it could not be seriously considered for use in an ointment, and the pure compound was not tested for irritancy in an ointment, in so far as is known, until the spring and summer of 1943. The representatives of NDRC were about to recommend the use of CC-2 in a protective ointment when the processes for producing S-330 and the fact of its nonirritancy were established in August 1943. The physical properties of CC-2 are not so satisfactory as either S-461 or S-330, from the standpoint of fabricating an ointment, and its low content of active chlorine makes it impossible to produce an ointment having more than about 1.5 per cent active chlorine.

Extensive searches have been made to find agents other than chloramides which will be effective in an ointment in protecting against H or other vesicants.[2,5,9,11,14,27,29] These searches have been carried on in England, and in several laboratories in this country under the auspices of NDRC, CMR, CWS, and the Naval Research Laboratory. The justification for this extensive search lay in the fact that, by their very nature, all chloramides are likely to be somewhat irritating when applied continuously or repeatedly to human skin. No compound other than a chloramide has been found which was sufficiently effective against H to justify its use.

An interesting outcome of attempts to improve the available ointments was the formulation of a protective ointment, similar to M-5, in which dimethyl phthalate replaced triacetin as the liquid vehicle. This ointment is apparently similar to M-5 in stability, lack of irritancy, and effectiveness of protection against H; in addition, it has the advantage of repelling mosquitoes for a period as long as 8 hours after the application of the ointment.[9,31,32]

Protective powders containing a chloramide were reported to be more satisfactory in the tropics, because of the lower irritancy, than were protective ointments. Powders containing S-461, having excellent characteristics with respect to covering and adhering to the skin, were prepared.[4] The powders were not irritating to the skin; however, they did not offer much protection as judged by the Edgewood cup method.[3] Powders containing a chloramide have not been evaluated for protection in a toxic chamber.

23.3 PROBABLE USEFULNESS OF PROTECTIVE OINTMENTS

The chloramide in a protective ointment reacts with H in such a way that one to three "active" chlorines are required to detoxify one molecule of H. In an ointment, the small amount of active agent that can be spread upon the skin has a rather negligible capacity for destroying droplets of liquid H. However, a film of a good ointment probably contains sufficient active chlorine to detoxify all of the H molecules impinging upon the surface during exposure of a few hours to concentrations of H vapor of the order of 20–30 μg of H per liter of air. Sufficient active chlorine for protection will remain upon the skin for a few hours, provided the ointment is applied to a relatively flat surface, such as on the inside of the forearm, and provided that the subject does not perspire too freely or that the ointment is not rubbed off by clothing or otherwise. Even under optimum conditions, a protective ointment can only be expected to reduce casualties and cannot long offer complete protection to the hands, neck, and face of men in combat.

There are considerable differences among dichloramine-T, CC-2, S-323, S-461, and S-330 as to the

length of the period during which the agent remains on the skin. The insoluble stable compounds, such as S-328, S-461, and S-330, apparently remain on the skin longer than does dichloramine-T. CC-2 suffers under the disadvantage, as compared with S-328, S-461, and S-330, of low content of active chlorine and sensitivity to light, so that some decomposition of the compound occurs in sunlight.[7] However, the persistence of protection of an ointment containing the more stable chloramides is in large part determined by the vehicle into which the ointment is incorporated.[17]

The duration of protection by an ointment is determined in large part by the exertions made by the subject during the period of his wearing the ointment; thus, the more vigorously the subject exercises, the more quickly will the protection be lost, especially on those portions of hands, jaw, and neck where there are sharp angles and creases in the surface of the skin.[17,34] Exercise and high temperature also increase the amount and extent of irritation caused by the use of a protective ointment.[3] In view of these variations, it is impossible to give any definitive picture of the amount of protection offered by a protective ointment, or of the extent of irritation on repeated application. The numerous reports listed in the Bibliography should be consulted if detailed information is desired as to the effectiveness and liabilities incidental to the use of representative protective ointments.

The following statements give a fair indication of the characteristics of the M-5 ointment containing S-330. An ointment containing S-330 may be applied 3 times a day for 3 successive days to the most sensitive areas of skin without significant irritation, if the men are exposed to temperatures which do not exceed 90 F at relative humidities not averaging above perhaps 70 per cent. Tests carried out in this country, as well as in Australia,[20,21,34,36] indicate that under these conditions almost none of the men wearing the ointment show any irritation. As the conditions more closely approach those of the tropics, the extent of irritation increases.[19,34,38] However, it has been concluded, as the result of tests carried out in Panama under rather severe conditions, that the M-5 ointment does not give too great an irritation to prohibit its use even in the tropics.[12] During 3 days of continuous wear in maneuvers in the jungle, the majority of soldiers were somewhat irritated. The irritation caused by M-5 is perhaps somewhat greater than when S-330 is used in the simpler vehicle of the S-461 Navy ointment.

It has been reported that, on the basis of the chamber tests at Edgewood Arsenal, men are protected for 1–2 hours against exposure to a concentration of H of around 30 μg / l of air, at a temperature of 90 F and 80 per cent relative humidity. One hour's exposure to a concentration of 30 μg l corresponds to a vapor dosage (*CT*) of 1,800 mg min m^3, i.e., (60 × 30).[18]

In chamber tests in Australia, the subjects after applying the ointment were exercised for different periods of time before being subjected to the chamber tests under temperature and humidity conditions similar to those employed at Edgewood Arsenal. All subjects were exposed to an H vapor dosage of 1,000 mg min m^3 and the relative protection provided by the ointments noted. It was found that the S-461 and S-330 ointments were markedly superior to the A.G. No. 5 ointment in having a much greater persistency of protection, that is, those subjects who exercised 1 or 2 hours before entering the chamber were still moderately well protected by these ointments, whereas the A.G. No. 5 ointment was practically valueless.[33,34]

No known protective ointment will give complete protection without irritation to any subject, but the M-5 ointment should materially reduce casualties in case men encounter H vapor in the field. It is the least irritating ointment on repeated application, with the possible exception of the British A.G. No. 5, although the latter may cause cyanosis.[36,39] The greater stability of M-5 on storage and the much greater persistence of protection as compared with A.G. No. 5 make it the best protective ointment so far produced.[21,38] M-5 ointment is also a good decontaminant for skin,[3,8] clothing, and weapons, and may be used in rendering clothing protective against H in case of emergency.

Chapter 26

CHLORAMIDE-IMPREGNATED TYPE OF PROTECTIVE CLOTHING

By *Homer Adkins* and *Wilkins Reeve*

26.1 INTRODUCTION

With the outbreak of war in 1941, the Armed Services faced critical problems in connection with the provision of gas-protective clothing for the enormous Army and Navy organizations planned. Peacetime research by the Chemical Warfare Service [CWS] had provided a chemical impregnation system for air-pervious clothing which made such clothing protective against mustard gas (H).[1] However, the unprecedented demands of global warfare, with respect to conditions of storage, use, and volume of clothing, necessitated radical modifications in both formulation and process.

The 1941 impregnating process was based on Impregnite CC-2, a chloramide containing available chlorine which reacts with H and thus protects against it. The clothing, including herringbone twill coveralls, OD wool uniforms, underwear, and accessories, was impregnated with a solution of CC-2 in hot tetrachloroethane (TCE) containing chloroparaffin (CP). The tetrachloroethane solvent was then evaporated, leaving the CC-2 bonded to the fabric by the viscous chloroparaffin. This "solution process" was operated in machine impregnating plants specially constructed to resist corrosion and provide for solvent recovery.[10] The clothing was baled for storage until needed.

Serious difficulties faced in early 1942 included the very limited life of baled impregnated clothing stored under tropical conditions,[11] unavoidable and dangerous delays in procuring enough of the complex solution-impregnating plants for global use, inadequate supplies of TCE, the necessity for transporting very large amounts of TCE, and hazard to operating personnel from toxic TCE vapors.[12]

The initial problem of preventing destruction of clothing impregnated with CC-2 was referred to the National Defense Research Committee [NDRC] by the Naval Research Laboratory [NRL] in February 1942. This problem was then assigned by NDRC to a research group. Contacts with activities of the Chemical Warfare Service were set up within a few weeks. Following the development of leads on the original problem, a second major objective was introduced, the development of an aqueous impregnation process. New problems subsidiary to this objective later became major research objectives in themselves. Meanwhile, the need for portable hand impregnating units was recognized and set up as an additional objective under the project. Throughout this work, NDRC and other Government agencies continued their efforts to make basic improvements in protective systems, including evaluation of newly synthesized impregnites, study of the intrinsic stability of fabrics, and development of superior binders and dispersing agents.

General programs involving the NDRC research group were planned in collaboration with the Technical Division of the Chemical Warfare Service at Edgewood Arsenal and the Naval Research Laboratory at Washington. The NDRC research was accompanied by development work at NRL and at Edgewood, some directly related to the NDRC program and some independent of it. Plant trials of new or modified processes derived from the NDRC research program were ordinarily conducted jointly by the Service and NDRC personnel, with the latter in the capacity of advisers and observers. Practical tests of a research character, such as troop wearing and hand impregnation trials, were planned jointly, administered by the Services, and usually observed by NDRC personnel. All gas chamber tests were Service-conducted. The engineering of standardized field impregnation plants and sets was handled by the Service organizations. In addition, representatives of the Quartermaster Corps were active in joint evaluation work on fabric quality. The probable protective values of fabrics were determined by laboratory methods by NDRC contractors, as well as at Edgewood Arsenal and the Naval Research Laboratory. Representatives of the U. S. Food and Drug Administration assisted in planning and in analyzing the results of wearing tests.

The problem of impregnating fabrics with CC-2 is rather complex since it involves applying a highly reactive chemical to fabric of uncertain chemical history and reactivity, and subsequently maintaining both the strength of the fabric and the activity of the

impregnate through long periods of storage and wearing service under adverse conditions. The circumstances required an impregnation process permitting immediate procurement of equipment and a reduction of supply transport to a minimum, and simple enough for field operation. The need was urgent, as adequate preparations for the protection of 8 9 million men required both impregnation of clothing for storage, and procurement of equipment for use in the Theaters of Operations (T of O) and in the actual combat zones.

The general object was to apply impregnite equivalent to 0.5 mg of available chlorine per square centimeter of fabric by the simplest possible procedure, in a formulation which would insure a useful life for both fabric and impregnite in storage and in use.

The major achievement in the project on the chloramide type of protective clothing has been the development and improvement of a process in which water replaces the organic solvent formerly required. The solution of this problem obviated the necessity for the procurement and transport of large quantities of tetrachloroethane, a result which was of particular importance in the T of O plants. The successful solution of the problem led to the development of easily transported hand impregnation sets for use by troops in the field. The field process has made protective clothing available for use by troops in combat areas, or in areas so isolated as to make impractical a supply of impregnated clothing from the T of O plants. The necessity for frequent reimpregnation in hot humid weather makes the field process fo impregnation particularly useful in tropical climates.[39]

Numerous corollary problems have been studied, and, in most instances, a practical solution obtained, e.g., grinding CC-2 to a fine particle size to permit stable suspensions and efficient reaction with H vapor;[8] discovery of dispersing agents resistant to the chemically reactive CC-2 and yet effective in emulsifying chlorinated paraffin and deflocculating CC-2 in all types of water,[5,6,22] elimination, for camouflage purposes, of the surface-whitening of fabrics caused by the aqueous dispersions;[15] tendering of cellulosic shipping containers by the finely divided CC-2 in powder form;[23] thermal sensitivity of powdered CC-2;[2] laundryfastness of impregnated fabrics;[19-21] methods for rapidly evaluating in the laboratory the characteristics of an impregnated fabric, which manifest themselves during storage and wear of garments under realistic conditions;[10,14] skin irritation accentuated by impregnated fabrics and improving the comfort of impregnated garments;[29] build-up of impregnation components on clothing during several periods of use and reimpregnation;[19,20] and stiffening of clothing by impregnation.

Attention has also been given to alternative impregnites,[26-28] with some attention to those that might be effective against the nitrogen mustards, as well as against H. The effect of the processing of textiles, prior to impregnation, upon the life of the impregnite and the impregnated fabric, have been investigated.[11,12,24,25] The results of the study of all these problems are given in the technical reports, but only a few are discussed here.

Of the major developments under the project, three were adopted by the Armed Services in 1942 and 1943; four were undergoing practical service tests by the Services when hostilities stopped; and one, upon which initial leads had been obtained, was referred to the Service laboratories for consideration.[39]

26.2 STABILIZATION OF FABRICS IMPREGNATED BY SOLUTION PROCESS[1,9,15,20,21,39]

Fabrics impregnated with CC-2 without any stabilizer lost practically all their tensile strength when stored in a simulated tropical storage room (46 C and 85 per cent RH) after a period of 3 months. Under the conditions of storage in the field, 0-33 per cent of the original tensile strength was retained after storage for 12 months. Similarly, all the positive chlorine was lost in the simulated tropical storage room during 3 months, whereas 0-76 per cent was retained in storage under field conditions.

The standard solution impregnation process developed by CWS was modified by dispersing in the tetrachloroethane solution of CC-2 about 10 parts of calcium carbonate per 100 parts of CC-2, with a suitable surface active agent, soya lethicin. The calcium carbonate concentration was adjusted so that the clothing picked up about 20 parts of calcium carbonate per 100 parts of CC-2. An alternative stabilizer, zinc oxide, developed under the NDRC program, was adopted by the Navy. They used 25 parts of zinc oxide based upon CC-2.

The process was adopted for use in the Zone of the Interior (Z of I) CWS plants in December 1943. Clothing impregnated by the new stabilized solution process, using calcium carbonate, retained 19 per

cent of its tensile strength after storage for 6 months in simulated tropical storage. After 3 months, 57 per cent of the active chlorine was retained, and, after 6 months, 27 per cent. Over 50 per cent of the tensile strength and 90 per cent of the active chlorine was retained by impregnated fabrics stored in the field for 12 months. The results with zinc oxide were significantly better, the retention of tensile strength being 86 and 76 per cent, and of active chlorine 66 and 43 per cent, after storage for 3 and 6 months, respectively.[39]

26.3 AQUEOUS SUSPENSION PROCESS FOR IMPREGNATING CLOTHING IN T OF O PLANTS[39]

The aqueous process is advantageous, as compared with the solvent process, for several reasons. There is a reduced requirement for procurement and transport of materials, since water locally available is used instead of the organic solvent, tetrachloroethane. About 50 million pounds of the solvent, tetrachloroethane, would have been required annually to take care of the *loss* of solvent incidental to the impregnation of the amount of CC-2 called for annually in the procurement program. The original requirement for solvent would have been much greater than 50 million pounds. The equipment required for the water process could be assembled rather quickly from standard laundry and dry cleaning machinery constructed of galvanized iron and steel, with wooden tanks. The solution process is quite corrosive and, therefore, required special equipment of strategic stainless steel, Monel, and aluminum, which could not have been obtained within the time limits. The water process is additionally advantageous in that there is no hazard to personnel from the dangerously toxic vapors of tetrachloroethane, and the use of water as a medium makes unnecessary a solvent recovery system.

In the process as developed, chloroparaffin is emulsified in a water solution of polyvinyl alcohol by recirculation through gear pumps; micronized CC-2 containing 10 per cent of its weight of zinc oxide (XX-CC-3) is similarly dispersed in this emulsion. The resulting concentrate is diluted for impregnation. Water dispersible pigments, developed for the purpose, are added for camouflage purposes. The proportion of ingredients is 100 parts XX-CC-3, 75 parts chlorinated paraffin, 5 parts polyvinyl alcohol, and 5 parts dispersible color.

The Navy also adopted the process, with formula changes to meet their conditions.[40] In the formula used by the Navy, the zinc oxide was increased to 25 parts per 100 parts of CC-2. The polyvinyl alcohol was decreased to 3.75 parts with 0.75 part of Daxad-11, 0.15 part of Duponol ME and 9 parts of dispersible color. Daxad-11 or Tamol NNO is naphthalene formaldehyde sodium sulfonate, and Duponol ME is a technical grade of sodium lauryl sulfate.

Fabrics stabilized with zinc oxide (10 per cent) and impregnated by the aqueous process retained 94 per cent of their tensile strength and 66 per cent of their active chlorine after storage for 3 months in simulated tropical storage. The corresponding figures for

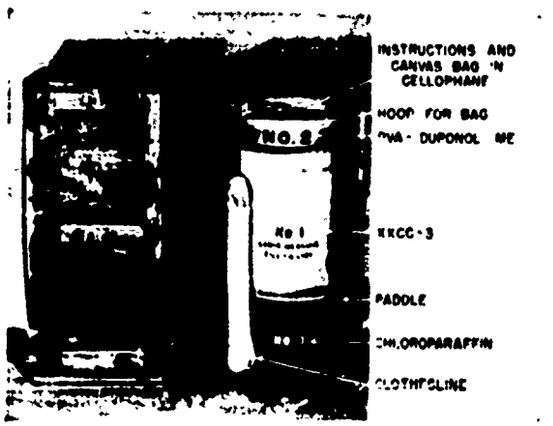


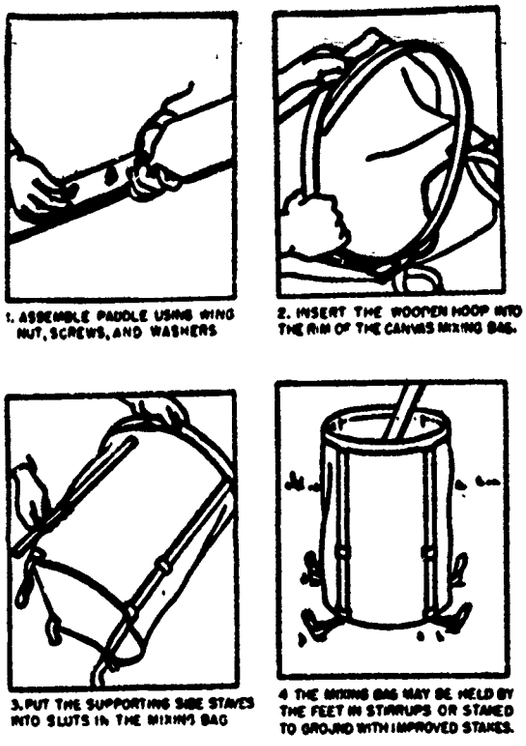
FIGURE 1. Field impregnating set, M-1.

6 months' storage are 75 and 38 per cent. The corresponding figures for calcium carbonate (20 per cent) are 47 and 41 per cent for 3 months, and 41 and 16 per cent for 6 months' storage.

26.4 GROUP IMPREGNATING SETS FOR USE BY TROOPS IN FIELD

26.4.1 M-1 Field Impregnation Set[3,4,7,38]

The development of a process for impregnation using water instead of an organic solvent made possible a process for impregnation of clothing by small groups in the field (Figure 1). All materials and equipment are contained in a plywood box weighing 80 pounds, and occupying 13.5 × 13.5 × 28 inches, or 2.9 cubic feet. The set provides for the impregnation of the protective clothing for 25 30 men at the standard loading of 0.5 mg of active chlorine per square centimeter of fabric. The mixing tank is a



TO MIX

Important: Use entire contents of each package.

Use marked container for measuring water. Pastes must be thick in Steps B and C.

A. Assemble paddle and canvas mixing bucket as illustrated. Empty in Package No. 1 *first*. Then sprinkle in Package No. 2. Mix the dry powders by stirring briskly for two (2) minutes.

B. Add two (2) *small* measures of water. Stir briskly for 15 minutes until all lumps are gone.

C. Add entire contents of Package No. 3. Stir the thick paste briskly for 20 minutes.

D. Fill the *large* measure with water and add package No. 4. Stir until lumps are gone, add the mixture slowly to thick paste in the canvas mixing bucket while stirring briskly. Stir in three additional *large* measures of water.

Important: Keep stirred and use at once.

TO DIP CLOTHES

Important: Soak large pieces of clothing first, and undershirts, socks, and gloves last. Always stir before dipping clothes.

1 — Soak and squeeze clothes in the mixture until wet through and through.

2 — Wring lightly over and into mixing bag. Do not waste material on the ground. Wring just enough to prevent dripping.

3 — Hang up to dry on clothesline or bushes, smoothing out wrinkles. Avoid sunlight if possible.

4 — Smooth out spots with hand or brush while clothes are wet.

FIGURE 2. Instructions for use of field impregnating set, M-1.

collapsible canvas bucket, the agitator a two-piece wooden paddle. The water requirement of about 23 gallons is measured in the top and bottom portions of the drum used for storage and transport of the CC-2. The box contains the required material in four packages, i.e., the micronized CC-2 with zinc oxide, the polyvinyl alcohol-Duponol mixture, the chlorinated paraffin, and the water-dispersible color. The formula used is 110 parts XX-CC-3, 75 parts polyvinyl alcohol, 0.5 part Duponol ME, 3 parts dispersible color. The XX-CC-3 and polyvinyl alcohol-Duponol are mixed dry. A measured quantity of water is added and the mixture converted to a thick paste by stirring. The chloroparaffin is added and emulsified by mixing with the thick paste. The camouflage pigment is dispersed in water and the paste diluted to the concentration desired for impregnation. The garments are immersed, squeezed until drip-free, and hung up in the air to dry (Figure 2).

The process is simple and has been repeatedly operated successfully by totally inexperienced personnel. Approximately 200,000 M-1 field impregnating sets were procured late in 1943, and have been stocked for Army, Navy, and Marine Corps personnel.[39]

26.4.2 Lightweight Simplified Field Set[13,37,39]

An improvement in the M-1 field impregnation set, called the lightweight simplified field set, has been developed. The set is 40 per cent lighter and 50 per cent smaller than the M-1. Making up the bath for impregnation is simpler and more rapid than in the case of the M-1.

In the simplified set, all the ingredients are mixed together with a measured volume of water in a canvas bag, mixed to a paste, and diluted to impregnating concentration. The time required is reduced in the simplified set to 25 minutes as compared with 1 hour for the M-1. The composition of the set is 100 parts of micronized CC-2 (i.e., XX-CC-2), 25 parts chloroparaffin, 10 parts Aresklene-400, and 6 parts dispersible color. The significant changes in

composition from the M-1 set is that chloroparaffin is reduced from 75 to 25 parts, the polyvinyl alcohol is replaced with Aresklene-400, and the stabilizer for the fabric (zinc oxide) is omitted. The stabilizer is omitted since the impregnated clothing would not be stored, and the omission makes possible not only a reduction in weight of materials transported, but also, more important, a somewhat increased stability of the impregnite on the fabric.

The tests carried out under the direction of the Naval Research Laboratory and the Marines have indicated that the simplified set meets their requirements.[37]

FIGURE 3. Helmet impregnating set.

26.5 INDIVIDUAL HELMET IMPREGNATING SET FOR USE BY TROOPS IN FIELD[25,32,33]

A package, formula, and process for use in individual impregnation of clothing has been developed (Figure 3). The composition is 110 parts of XX-CC-2, 25 parts chloroparaffin, 10 parts Aresklene-400, and 6 parts dispersible color. The package is 1.75x 3x3 inches in dimension, and weighs 0.43 pound. The XX-CC-3 is placed in a lacquer-lined steel can, the parts of which serve for measuring the water. The chloroparaffin and Aresklene are contained in sealed lead tubes embedded in the micronized CC-2 (XX-CC-2). The instructions are printed on the outside of the container and state that the contents of the tubes and the XX-CC-2 are to be dumped into the helmet, using a measured volume of water. After a mixing by hand, water is added, and the impregnation is carried out by immersing the garment, part by part, in the helmet and wringing.

The set is attractive because of ease of transport, by air or otherwise, and because of the simplicity of operation, permitting it to be used by untrained troops in whatever number may be desired. The set has been tested by representatives of both the Army and Navy with respect to make-up and protection in a toxic chamber, and appears to be satisfactory.[47]

26.6 ALTERNATE STABILIZERS, BINDERS, AND AGENTS FOR AQUEOUS-SUSPENSION PROCESS[39]

Results have been obtained which indicate that the aqueous suspension process used in the T of O equipment may be advantageously modified in certain respects. There is some evidence that calcium carbonate is to be preferred to zinc oxide as a stabilizer for fabrics in the impregnation process. Calcium carbonate is apparently somewhat less effective than zinc oxide in preventing tendering of the fabric, if it is used in the same concentration as is zinc oxide. However, when used in somewhat higher amounts, e.g., 20 parts of calcium carbonate per 100 parts of CC-2, it is equally effective.[18,31] The presumed advantage of calcium carbonate is that clothing carrying this stabilizer causes somewhat less irritation when worn under tropical conditions than clothing carrying zinc oxide.[39]

The addition of zinc oxide or calcium carbonate in the impregnation process unquestionably increases the life of the garments, particularly if they are stored under tropical conditions.[1,9,18,31] However, although the stabilizers are effective in extending the life of the fabric, they reduce the life of the impregnite on the fabric during wear.[30,32] It appears that the omission of the fabric stabilizer would be advantageous in actual field impregnation when no clothing storage is involved. There is strong evidence that loss in positive chlorine is somewhat less rapid when no fabric stabilizer is present.

Extensive tests have indicated that the amount of chloroparaffin used in the standard impregnation processes can be reduced to one-third of that now recommended without any disadvantage.[16,20] Tests at the Naval Research Laboratory have confirmed this conclusion, and the Navy has adopted the use of 35 parts of chloroparaffin instead of the 75 parts per 100 parts of CC-2 hitherto used by the Army and the Navy.[36]

Attempts have been made to develop alternative agents in seeking possible improvements, as well as to guard against possible failure in the supply of chloroparaffin, polyvinyl alcohol, and CC-2. Several

grades of mineral oil have been found to be equivalent to chloroparaffin in binding action and, in some cases, the fabrics so impregnated showed a superior laundering resistance to those carrying chloroparaffin. However, the advantages demonstrated do not indicate that chloroparaffin should be replaced as the standard binding agent.[16,17]

Methocel (methylcellulose) and Aresklene-400 (dibutylphenylphenol sodium disulfonate) appear to be applicable to the T of O aqueous process, but they offer no apparent advantage and are somewhat more difficult to control in the plant process.[6,22] Aresklene-400, however, appears to be more satisfactory as a surface active agent for use in field sets, and is recommended for use in the simple lightweight field set referred to above. Methocel might also be used for this purpose, but a granular form of this agent, such as must be used in the field set where rapid solution is essential, was not commercially available in 1945.

In 1942 especially, a great deal of attention was given to the evaluation and development of processes for utilizing impregnites other than CC-2.[22,23] The reasons for this attention have been discussed in some detail in Chapter 24. The objectives sought in new impregnites were to obtain a cheaper and a more available compound than CC-2; to provide against a possible inadequate supply of CC-2 or the discovery of some such fatal weakness as was found in 1944 for the standard British Impregnite E;[49-52] or to obtain an impregnite which was less active than CC-2 in bringing about a tendering of the fabric, or which offered a greater or more permanent protection after impregnation. Agents were also sought, such as S-136, which would offer protection against nitrogen mustards as well as against H. In the end, none of the impregnites to which attention was given (i.e., S-328, S-461, S-210, and S-330) proved to have any significant advantage over CC-2; moreover, the improvement in the process and quality of CC-2, and the absence of gas warfare, made the results of the investigation of these impregnites appear to be of only historical interest.

26.7 IMPREGNATING SYSTEMS RECOMMENDED FOR FURTHER EVALUATION

When hostilities closed in August 1945, several modifications of the standard impregnating processes had been indicated by the results of research and tests already carried out. The representatives of NDRC at that time suggested that six different systems be more thoroughly evaluated and compared in troop wearing trials and in chamber performance, with the objectives of ascertaining possible advantages in lowered irritation and longer or more complete protection. These tests should be made under hot and humid conditions with troops living under field combat conditions. For reasons indicated in another section of this summary (Chapter 30), all garments should be made from one uniform lot of fabric, so that unequivocal conclusions may be drawn from the results of the test. Clothing impregnated by the following processes is suggested for the tests:

1. CC-2/ZnO/CP/PVA 100/10/75/5 — Standard aqueous system
2. CC-2/$CaCO_3$/CP 100/20/75 — TCE stabilized solvent system
3. CC-2/CP/no stabilizer 100/75/0 — TCE solvent system (1941)
4. CC-2/CP/PVA/no stabilizer 100/25/5/0
5. CC-2/CP/Aresklene/no stabilizer 100/25/10/0
6. CC-2/$CaCO_3$/CP/PVA 100/20/25/5

The group of six processes includes fabrics impregnated by the three standard systems for purposes of comparison with three newer systems. The results of the tests would show: the effect of omitting the stabilizer for the fabric or of reducing the chloroparaffin from 75 to 25 parts per 100 parts of CC-2; the effect of Aresklene-400 as compared with polyvinyl alcohol as an emulsifying and dispersing agent; and the relative merits, as judged by irritancy, of calcium carbonate and zinc oxide as stabilizers for the fabric. The results of the tests would also establish the length of time before reimpregnation of fabrics, originally impregnated by different processes and compositions, becomes necessary. Some of the questions referred to just above have been answered to the satisfaction of representatives of one Service, but not of the other. The results of such wearing trials, under realistic conditions, would serve to confirm or reject tentative conclusions resulting from extensive laboratory research

26.8 UNSOLVED PROBLEMS

Fabrics impregnated with CC-2 more or less rapidly lose their content of the active agent, i.e., positive chlorine, during storage and wear. Under the very severe conditions of wear in the tropics, the impregnated fabrics are perhaps not sufficiently protective for more than a week after impregnation.[30,33,53]

The extension of the effective life of the impregnite upon the fabric is perhaps the most serious unsolved problem in connection with protective fabrics carrying a chloramide for protection against H. This problem is intimately connected with another, i.e., the selection of fabrics which will allow the maximum life of the impregnite. Experience has shown that there is a great variation in the length of life of the impregnite, depending upon the process to which the fabric has been subjected prior to impregnation.[34,35]

At the time when the chief problem appeared to be the preservation of the tensile strength of the fabric during storage, fabrics from certain mills were selected as the best for impregnation. This was done after extensive surveys of fabric samples from all producers of herringbone twill had apparently shown that lightly processed textile fabrics retained their tensile strength better and longer than did more completely processed fabrics. However, this selection was made upon the basis of impregnation with an *unstabilized* solution system, as used in 1941, but no longer used by either of the Services.[32] Introduction of calcium carbonate or zinc oxide as a stabilizing agent practically eliminated this difference in tensile strength between fabrics of different sources. Recent surveys have shown that certain more completely processed textile fabrics, impregnated by the stabilized aqueous system, retained their chlorine much better than did some of the lightly processed fabrics just referred to.[36] It is clear that any worth-while studies, looking towards the prolongation of impregnite life of a fabric, must start with and be based upon fabrics of uniform and reproducible characteristics.

Patch wearing tests suggest that the use of zinc oxide or calcium carbonate in the aqueous system reduced chlorine retention during wear by about 20 per cent, so that it appears that, where garments are not to be stored, the stabilizer for the fabric should be omitted.[33] This lead has been followed in the formula recommended for the simplified lightweight field set and the helmet set. Patch wearing tests have indicated that the effect of the stabilizer, at least in the aqueous process, can be minimized by adding an acidic agent, like alum, to the impregnating system.[30] The validity of patch wearing tests as a guide to research has not yet been established by a close correlation with the results of sufficiently controlled troop wearing tests.[32] It appears that a fruitful approach to the problem of increasing the life of the impregnite on the fabric depends upon carefully planned wearing tests carried out under realistic conditions. It is essential in such studies, if useful results are to be obtained, that the fabric variable be held constant. Lack of control of the fabric variable, unavoidable at the time, is a weakness which may vitiate the results of previous wearing trials in which chlorine retention was determined.

Chapter 27

PREPARATION OF CARBON-TREATED FABRICS

By Homer Adkins and Wilkins Reeve

27.1 INTRODUCTION

THE INVESTIGATION of methods of incorporating activated carbon into cotton fabrics was prompted by knowledge that the British had developed a process for the preparation of carbon-containing fabrics which used rubber latex as the binding agent, and that they were studying this process in 1941 on a plant scale.[30,32] In this country, three fundamentally different approaches to the problem were developed. The first involves impregnating piece goods or the finished garments with activated carbon dispersed in a suitable medium. The second involves applying the activated carbon to the piece goods by a coating process using viscose as a binding agent. The third involves incorporating the activated carbon into viscose rayon yarn during the preparation of the yarn and prior to the weaving of the fabric. All three processes are suitable for the preparation of carbon garments on a large scale, and each has certain advantages and limitations. The first process, as applied to garments, was not developed until shortly before the end of hostilities and hence has been very inadequately studied; it appears to be an excellent method for applying activated carbon to fabrics which are in the form of garments. Plant methods for the impregnation of cotton piece goods with activated carbon are less desirable than the second method involving the coating of the fabric. The second process is technically suitable for the application of activated carbon to a large fraction of the cotton twill fabric procured for outer garments. The treated fabric is of high quality, and the processing cost is low. The third process enables a larger amount of carbon to be incorporated per unit area of fabric. The fabrics have relatively good textile properties (color, hand, drape, etc.) but are more expensive to prepare and do not wear so well as standard untreated cotton twills.

Carbon fabrics* are expected to be of increasing importance in providing protection against chemical warfare agents because (1) protection is provided against all types of vesicants instead of being specific for those agents which are destroyed by the chloramide type of impregnite, (2) the protection provided against H [*bis*(β-chloroethyl) sulfide] is of a similar order to that provided by chloramide-impregnated clothing, (3) the protection provided against vapors of HN1 [ethyl *bis*(β-chloroethyl)amine] and HN3 [*tris*(β-chloroethyl)amine] is superior to that provided by chloramide-impregnated clothing, and (4) in the future, it may be economically and technically more feasible to provide carbon clothing than chloramide-treated clothing.

27.2 CHOICE OF MATERIALS

27.2.1 Adsorbents

Activated carbon is the only adsorbent which has been used in the work carried out in this country. Preliminary studies carried out by the British have shown that certain inorganic sulfides strongly adsorb H, even from organic solvents.[31] These might be given serious consideration in future research work. Their work has shown silica gel and adsorbent alumina to be inferior to activated carbon.[30]

The protective properties of fabrics containing activated carbon are dependent on the adsorptive properties of the activated carbon in the fabric, which in turn are dependent on the method by which the activated carbon is prepared.[1] The adsorptive capacity effective under conditions of use is only a small percentage of the total adsorptive capacity and is not necessarily a function of the latter. It is believed the geometrical arrangement of the carbon surface within the carbon particle is of considerable importance. The carbon particles consist of a network of large macropores through which all gases can diffuse, micropores opening into the macropores, and sub-micropores opening into the micropores. Activated carbons prepared by different procedures have their surface areas distributed differently among the various pores; for this reason, each gas has a characteristic adsorption isotherm for each type of carbon, and the relative adsorptive properties of two different carbons may vary depending on the partial pressure of the adsorbed gas at which comparisons are made.

*By "carbon" fabrics or garments is meant "carbon-treated" fabrics or garments.

The extension of the effective life of the impregnite upon the fabric is perhaps the most serious unsolved problem in connection with protective fabrics carrying a chloramide for protection against H. This problem is intimately connected with another, i.e., the selection of fabrics which will allow the maximum life of the impregnite. Experience has shown that there is a great variation in the length of life of the impregnite, depending upon the process to which the fabric has been subjected prior to impregnation.[34,35]

At the time when the chief problem appeared to be the preservation of the tensile strength of the fabric during storage, fabrics from certain mills were selected as the best for impregnation. This was done after extensive surveys of fabric samples from all producers of herringbone twill had apparently shown that lightly processed textile fabrics retained their tensile strength better and longer than did more completely processed fabrics. However, this selection was made upon the basis of impregnation with an *unstabilized* solution system, as used in 1941, but no longer used by either of the Services.[17] Introduction of calcium carbonate or zinc oxide as a stabilizing agent practically eliminated this difference in tensile strength between fabrics of different sources. Recent surveys have shown that certain more completely processed textile fabrics, impregnated by the stabilized aqueous system, retained their chlorine much better than did some of the lightly processed fabrics just referred to.[36] It is clear that any worth-while studies, looking towards the prolongation of impregnite life of a fabric, must start with and be based upon fabrics of uniform and reproducible characteristics.

Patch wearing tests suggest that the use of zinc oxide or calcium carbonate in the aqueous system reduced chlorine retention during wear by about 20 per cent, so that it appears that, where garments are not to be stored, the stabilizer for the fabric should be omitted.[33] This lead has been followed in the formula recommended for the simplified lightweight field set and the helmet set. Patch wearing tests have indicated that the effect of the stabilizer, at least in the aqueous process, can be minimized by adding an acidic agent, like alum, to the impregnating system.[30] The validity of patch wearing tests as a guide to research has not yet been established by a close correlation with the results of sufficiently controlled troop wearing tests.[32] It appears that a fruitful approach to the problem of increasing the life of the impregnite on the fabric depends upon carefully planned wearing tests carried out under realistic conditions. It is essential in such studies, if useful results are to be obtained, that the fabric variable be held constant. Lack of control of the fabric variable, unavoidable at the time, is a weakness which may vitiate the results of previous wearing trials in which chlorine retention was determined.

Chapter 27

PREPARATION OF CARBON-TREATED FABRICS

By *Homer Adkins* and *Wilkins Reeve*

27.1 INTRODUCTION

THE INVESTIGATION of methods of incorporating activated carbon into cotton fabrics was prompted by knowledge that the British had developed a process for the preparation of carbon-containing fabrics which used rubber latex as the binding agent, and that they were studying this process in 1941 on a plant scale.[29,32] In this country, three fundamentally different approaches to the problem were developed. The first involves impregnating piece goods or the finished garments with activated carbon dispersed in a suitable medium. The second involves applying the activated carbon to the piece goods by a coating process using viscose as a binding agent. The third involves incorporating the activated carbon into viscose rayon yarn during the preparation of the yarn and prior to the weaving of the fabric. All three processes are suitable for the preparation of carbon garments on a large scale, and each has certain advantages and limitations. The first process, as applied to garments, was not developed until shortly before the end of hostilities and hence has been very inadequately studied; it appears to be an excellent method for applying activated carbon to fabrics which are in the form of garments. Plant methods for the impregnation of cotton piece goods with activated carbon are less desirable than the second method involving the coating of the fabric. The second process is technically suitable for the application of activated carbon to a large fraction of the cotton twill fabric procured for outer garments. The treated fabric is of high quality, and the processing cost is low. The third process enables a larger amount of carbon to be incorporated per unit area of fabric. The fabrics have relatively good textile properties (color, hand, drape, etc.) but are more expensive to prepare and do not wear so well as standard untreated cotton twills.

Carbon fabrics* are expected to be of increasing importance in providing protection against chemical warfare agents because (1) protection is provided against all types of vesicants instead of being specific for those agents which are destroyed by the chloramide type of impregnite, (2) the protection provided against H [*bis*(β-chloroethyl) sulfide] is of a similar order to that provided by chloramide-impregnated clothing, (3) the protection provided against vapors of HN1 [ethyl-*bis*(β-chloroethyl)amine] and HN3 [*tris*(β-chloroethyl)amine] is superior to that provided by chloramide-impregnated clothing, and (4) in the future, it may be economically and technically more feasible to provide carbon clothing than chloramide-treated clothing.

*By "carbon" fabrics or garments is meant "carbon-treated" fabrics or garments.

27.2 CHOICE OF MATERIALS

27.2.1 Adsorbents

Activated carbon is the only adsorbent which has been used in the work carried out in this country. Preliminary studies carried out by the British have shown that certain inorganic sulfides strongly adsorb H, even from organic solvents.[31] These might be given serious consideration in future research work. Their work has shown silica gel and adsorbent alumina to be inferior to activated carbon.[30]

The protective properties of fabrics containing activated carbon are dependent on the adsorptive properties of the activated carbon in the fabric, which in turn are dependent on the method by which the activated carbon is prepared.[11] The adsorptive capacity effective under conditions of use is only a small percentage of the total adsorptive capacity and is not necessarily a function of the latter. It is believed the geometrical arrangement of the carbon surface within the carbon particle is of considerable importance. The carbon particles consist of a network of large macropores through which all gases can diffuse, micropores opening into the macropores, and sub-micropores opening into the micropores. Activated carbons prepared by different procedures have their surface areas distributed differently among the various pores; for this reason, each gas has a characteristic adsorption isotherm for each type of carbon, and the relative adsorptive properties of two different carbons may vary depending on the partial pressure of the adsorbed gas at which comparisons are made.

The four processes which have been used for the preparation of activated carbon on a large scale for use in canisters are as follows:

1. Wood zinc chloride process. Wood in the form of sawdust is impregnated with zinc chloride, heated, and extruded under high pressure. The volatilization of the zinc chloride on pyrolysis causes the necessary pore structure to form and also activates the carbon. This carbon was produced by the National Carbon Company and is known as National carbon.

2. Carbonization of coal. Pulverized coal is carbonized in retorts and activated with steam. The activated carbon so produced is characterized by a high density and a relatively high (20 per cent) ash content. This carbon was produced by the Pittsburgh Coke & Chemical Company and is known as PCC (or PCI from an earlier name of the company) activated carbon.

3. Carbonization of sawdust briquettes. The sawdust is treated with pitch and formed into briquettes. These are carbonized under pressure and the resulting carbon activated with steam. This process was employed by the Crown-Zellerbach Company, and the material is known as Carlisle carbon.

4. Carbonization of nut hulls. Nut hulls from a variety of nuts are carbonized and the carbon activated with steam. The final product is not so uniform as the carbons described above because of the nonuniformity of starting materials. This carbon was made by the Barneby-Cheney Company and is known as Barneby-Cheney carbon.

For use in canisters, the above types of carbon are "whetlerized" with certain heavy metal salts to increase the protection provided against certain nonpersistent chemical warfare agents; however, whetlerized carbon was not used in the protective clothing work inasmuch as none of the nonpersistent agents are vesicants. Since unwhetlerized National carbon had a larger surface area than the other unwhetlerized carbons but was less satisfactory after whetlerization than the others, it was more available and appeared to be more suitable for the protective clothing work than the other types. Nearly all experimental work was carried out with two different lots of this material. One was known to Division 9 investigators as N-44 and represented the material produced in the Chemical Warfare Service's [CWS] plant, Fostoria, Ohio, from the summer of 1942 until the summer of 1943. The other, designated N-182, was produced at the same plant from January to March 1944.

Activated unwhetlerized National carbon as produced for eventual use in canisters has a particle size range of 12 30 mesh. The grinding of this material is difficult because of the hardness of the carbon. The material can be "micronized" with steam to an average particle size of 3 5 μ,[3] or it can be hammer-milled and air-classified so that the particle size range is approximately 10 30 μ.[7] It has been observed that the PCC carbon is too hard to be successfully hammer-milled without undue wear on the grinding equipment. Other types of equipment, such as Raymond mills, have not been investigated but should be suitable for the grinding of all types of carbon.

27.2.2 Binders

A binder must be used to make the activated carbon adhere to the fabric. In the case of the synthetic fibers containing activated carbon, the fiber itself acts as the binder. The binder must hold the carbon sufficiently firmly so that crocking (rubbing off of carbon) does not occur, and must not seriously decrease the adsorptive capacities of the activated carbon. The following types of binders have been tried.

1. Rubber latex. Natural rubber latex was used by the British[27,32,33] for the impregnation of woolen garments. Synthetic latexes have also been investigated. The former was unavailable during the war years and, in addition, underwent a slow decomposition with the formation of products which slowly deactivated the carbon. This caused the effectiveness of the carbon garments to decrease during storage.

2. Cellulose. Regenerated cellulose is the best binder now known for the coating of fabric with carbon. A solution of the sodium xanthate salt, as used for the manufacture of rayon, is mixed with carbon, coated on the fabric, and converted to regenerated cellulose by treatment with acid.[7] In the preparation of carbon-rayon yarn, the carbon is likewise mixed with the sodium xanthate cellulose solution and extruded through spinnerets into an acid bath to regenerate the cellulose.[2,3]

3. Alkali-soluble zinc cellulose. This has been used as a binder in the impregnation of piece goods[2] and garments[13] with activated carbon.

4. Cellulose derivatives and related products. A variety of cellulose derivatives including methylcellulose, ethylcellulose, hydroxyethylcellulose, and carboxymethylcellulose sodium salt have been investigated as binders and all found to have little effect

on the activity of the carbon,[2,5,6,13] providing the ratio of binder to the carbon is sufficiently low so that the carbon is not covered by a continuous film. Methyl- and ethylcellulose can be used directly. In the other cases, the binding agent is converted into a water-soluble form by alkali, and treated with acid to regenerate the material after application to the fabric. Cellulose acetate filaments containing activated carbon [25] have been spun but do not appear promising.

5. Various pectic acid salts.[1] These do not poison the carbon, but the carbon is not bound sufficiently firmly to prevent crocking. Natural and synthetic gums,[1] various types of starches and starch acetate,[5] chitin,[5] and chlorinated starch [13] have also been tried.

6. Protein products. Casein has been used as a binder for the impregnation of fabrics [1,2,5] and garments [13,14] with carbon. The casein is insolubilized by treatment with formaldehyde or lime. In the former case, the crocking properties are satisfactory, but formaldehyde is difficult to handle on a plant scale, and the garments are excessively stiff. In the latter case, the carbon crocks excessively. Other materials tried include maizein [1] and chrome gelatin.[2]

7. Synthetic polymers. Synthetic filaments containing activated carbon have been prepared from copolymers of vinyl chloride and other vinyl compounds,[26] and laboratory and arm-chamber tests indicate that carbon retains most of its activity.[4,21] Since manufacturing facilities for the preparation of large quantities of this type of synthetic yarn were not available, these materials were not developed.

Polyvinyl alcohols, polyvinyl chloride, and polyvinyl acetate have been tried as binders for the impregnation of fabrics and garments with carbon.[2,5,13] Polyvinyl esters differ from the previously discussed binders in that the H is soluble in the polymer. The above compounds are excellent binders insofar as binding the carbon to the fabric is concerned; however, the activity of the carbon fabrics, as measured in the laboratory, appears inferior. Other synthetic polymers include polybutene,[2,5,6] Carbowax,[5] acrylates,[1] methacrylates,[1,5] alkyd resins,[1] urea-formaldehyde resins,[1,13] melamine-formaldehyde resins,[13] and modified styrene maleic anhydride interpolymers.[5]

Copolymers of ethyl and methyl acrylate have been tried in connection with the impregnation of piece goods with activated carbon.[1,2] The carbon is firmly bound, but the activity of the carbon is much reduced, unless "protected" by a prior treatment with an alginate salt.

8. Miscellaneous binders. Miscellaneous binders include sodium silicate [1] and chlorinated paraffin wax.[6,13]

27.2.3 Fabrics

In the case of the coated and impregnated materials, nearly all work in this country has been done with herringbone twill and Arnaen cloth. Both are 8- to 8½-ounce, tightly woven, snag-resistant, cotton twills. The first is procured by the Army for the preparation of standard cotton Army battle dress, regardless of whether or not it is to be made gas-protective. The latter is a higher quality, more expensive fabric which is procured by the Navy for the preparation of the specially designed Navy gas-protective suit. Arnaen cloth differs from herringbone twill in that (1) there are minor differences in details of construction, (2) it is not dyed, (3) it is much more uniform because it is manufactured and processed by only one company, and (4) it is subjected to relatively light processing in the finishing plant.

A few hundred yards of a lightweight "80 square" print cloth have also been coated with carbon, but there appears to be no military need for such material.

In the case of the carbon-rayon fabrics, woven and knit fabrics were prepared which had constructions different from the standard materials used by the Armed Services. These will be discussed in the section dealing with the preparation of the carbon-rayon materials.

27.3 PREPARATION OF CARBON-IMPREGNATED FABRICS

27.3.1 Introduction

Garments may be impregnated with carbon by immersion in a suitable dispersion of the carbon. Such a procedure has the advantage that the carbon is incorporated into the finished garment and makes it possible to impregnate the large number of garments held in storage by the Quartermaster. The choice of a suitable binding-dispersing agent depends on the relative importance of having a method of impregnation easily applied in the field as opposed to a more complex impregnation procedure requiring mechanical equipment, even though the garments impregnated by the former procedure are inferior to those prepared by the latter. In order for an impregnation procedure to be suitable for use by the average

soldier under field conditions, it is considered necessary that a single impregnating bath be employed and that this consist of an aqueous dispersion. The elimination of organic solvents and of two-step processes prevents the use of many attractive binders. Nevertheless, several aqueous one-bath systems have been developed containing calcium caseinate,[14] various cellulose derivatives,[5,6] and polyvinyl alcohol [5] as binders. Practical wearing tests on the most promising of the methylcellulose aqueous systems demonstrated that noticeable amounts of carbon are rubbed off under wet field conditions.[23]

By the end of hostilities, a formulation involving the use of ethylcellulose as a binder dissolved in tetrachloroethane had been developed on a laboratory scale. It is believed this impregnation procedure might prove to be suitable for use in the Army's M-1 Theater of Operations' (T of O) solvent CC-2 impregnating plants. The fabrics were outstanding with respect to softness, H vapor resistance in both the wet and dry conditions, and lack of cracking properties.[6]

Several more complex processes were developed prior to the above work. The original British development [27] involved (1) the thorough impregnation of the fabric with activated carbon, (2) the removal of the surface carbon by scrubbing, and (3) the thorough binding of the carbon in the fabric with rubber latex. It was the knowledge of this process that led to the undertaking of a research program in this country on carbon fabrics.

A somewhat similar method was developed in this country for the impregnation of piece goods with carbon dispersed in a zinc ammonium alginate solution. After impregnation, the surface carbon is removed by scrubbing, and an aqueous dispersion of a polyacrylate resin is applied to bind the carbon in the fabric.[1,2] The method is believed to be less practical than that employed in the preparation of the carbon-coated fabric.

A two-step process for the impregnation of garments was developed which involved the use of casein as a binding-dispersing agent followed by a second step in which the casein was insolubilized by exposing the impregnated garment to the vapors of formaldehyde overnight at room temperature.[13] The use of formaldehyde was inconvenient, especially on a plant scale, and the process was discarded because it was believed the number of garments which could be treated per day in the Army's M-2 T of O plant would be too low to be practical.

27.3.2 Preparation and Camouflage of Carbon

A study has been made of the relationship between particle size of the carbon and resistance to removal from the impregnated fabric by crumpling and water leaching. Fabrics impregnated with N-182 National carbon dispersed in an aqueous methylcellulose or hydroxyethylcellulose-glyoxal system exhibited greatly increased washfastness as the weight median diameter was reduced to 3 μ. A fabric impregnated with a methylcellulose system containing 22-μ carbon retained 16 per cent of its carbon after crumpling and water leaching as determined by H vapor capacity measurements, whereas a similarly impregnated sample with 3-μ carbon retained 100 per cent. It was concluded that the carbon to be used in the impregnation of garments should be as finely ground as is commercially practical.[5] Most of the laboratory work was carried out with micronized N-182 National activated carbon having a weight median diameter of 5 μ.

The carbon in the coated fabric or the impregnated garment can be camouflaged by incorporating in the carbon-binder mixture either "Mapico lemon yellow" iron oxide pigment or white titanium dioxide.[5,7,12] After impregnation with a carbon dispersion containing 75 parts yellow pigment per 100 of carbon, herringbone twill garments still have an olive drab shade which is only slightly darker than the original. White Arnaen cloth impregnated with a carbon dispersion containing 50 parts titanium dioxide per 100 of carbon is an attractive blue-gray shade.

27.3.3 Impregnation with Carbon from Aqueous Methylcellulose-Carbon Dispersions [5]

In its present state of development, the aqueous methylcellulose system does not meet the desired goal of complete resistance to removal by water, but it is believed to have sufficient water resistance to be useful in case of necessity. In a troop wearing trial, the skins of the troops wearing the clothing were badly darkened by carbon which rubbed off when exposed to a heavy downpour of rain.[23] Laboratory H resistance data also indicate the H vapor capacity of the fabric to be considerably lowered when wet. A preliminary chamber evaluation indicated that new garments provide protection for approximately two-thirds the length of time provided by carbon-coated garments.[24]

The preferred system consists of 100 parts mi-

cronized N-182 carbon, 25 parts 100 cps methylcellulose, 25 parts "Mapico lemon yellow" iron oxide pigment, and 1 part Tamol NNO (naphthalene formaldehyde sodium sulfonate). It is readily formulated by dissolving the fibrous methylcellulose (2.5 pounds) in 10 parts of water by hand stirring for several hours and then diluting to a 5 per cent solution. The concentrated suspension is prepared by blending the solid ingredients into the methylcellulose solution and hand stirring about 1 hour. The suspension is diluted with water to 0.5 per cent carbon. A bath so prepared is sufficient to impregnate approximately 25 uniforms. The wet clothing is wrung by hand until it ceases to drip and is then dried in a tumble drier. The clothing contains approximately 3 mg of carbon per square centimeter.

The investigation of this system was terminated before it could be developed completely. The system is not now in a practical state of development, but further laboratory work should indicate methods by which the present deficiencies can be overcome.

In the development of the above system, a large number of alternative binders were investigated. These included water-soluble binders such as hydroxyethylcellulose, polyvinyl alcohol, corn and potato starch, casein, zinc ammonium polymethacrylate, ammonium alginate, carboxymethylcellulose sodium salt, Daktose (deacylated chitin) acetate, Carbowax 1500, modified styrene maleic acid interpolymer, melamine-formaldehyde resin, urea-formaldehyde resin, and Swiss gum; and water-insoluble binders such as polyvinyl acetate, polyvinyl alcohol, polybutene, chlorinated paraffin, and ethylcellulose.

27.3.4 Impregnation with Carbon Dispersed in Tetrachloroethane Solution of Ethylcellulose [6]

Herringbone twill fabrics impregnated with activated carbon from suspensions in organic solvents containing ethylcellulose as a binder and dispersing agent have exhibited high H capacity under laboratory conditions, nearly complete leach and wash resistance, and little tendency to dust when crumpled. The preferred formulation has the composition 100 parts micronized N-182 carbon, 25 parts ethylcellulose (10 cps), 75 parts "Mapico lemon yellow" iron oxide pigment, 1,540 parts tetrachloroethane.

The impregnating suspension is prepared by dissolving 158 g ethylcellulose in 9,736 g tetrachloroethane with vigorous agitation at room temperature. The binder dissolves completely in about 15 minutes, and 625 g micronized carbon and 474 g iron oxide pigment are then added and stirring continued for 30 minutes. The fabrics are soaked in the impregnating suspension and then wrung to 400 g wet pickup (175 per cent) and dried by tumbling at 80 C. The impregnated fabric contains about 3 mg carbon per square centimeter.

The fabrics are relatively soft, and are of an olive drab shade only slightly darker than the OD7 of the original herringbone twill. With Armaco cloth, an attractive blue-gray shade is produced by substituting 50 parts titanium dioxide for the 75 parts of iron oxide. H capacity values determined in the laboratory are approximately three-fourths those obtained with the carbon-coated herringbone twill. Tests run on wet samples indicate that the adsorptive capacity is not impaired by the presence of water. Leaching the fabrics with water or laundering with 0.2 per cent Kalyc-A (an inorganic detergent consisting of 75 per cent sodium metasilicate and 25 per cent tetrasodium pyrophosphate) removed practically no carbon and did not lower the H capacity values.

The laboratory investigations were terminated before the system was developed completely; however, it appears extremely promising and should be investigated in plant equipment, in wearing trials, and in chamber tests.

27.3.5 Preparation of Carbon-Impregnated Woolen Fabrics with Rubber Latex Binder [27,32,33]

The use of rubber latex as a binder for carbon was not studied in this country because of the shortage of this material and because the earlier British work indicated that a slow decomposition of the rubber occurred with consequent poisoning of the carbon. The process is more adaptable to relatively thick woolen fabrics than it is to closely woven, thin cotton fabrics such as herringbone twill.

The impregnation bath, as used by the British in 1942, consists of 10 per cent activated carbon, 1 per cent rubber latex, lesser amounts of methylcellulose to serve as a stabilizing colloid, and Perminal WA (an I.C.I. Ltd. product) to improve penetration of the fabric. The fabric is dried to complete primary fixation and is then thoroughly washed to remove superficial and loosely adhering carbon. The carbon is then more thoroughly fixed by dipping the fabric in a 1 per cent Positex dispersion and drying.

The Positex used was obtained by the addition of Lissolamine A to a commercially vulcanized latex

(Revultex) to the extent of 7.5 per cent of the dry rubber content. The binding action depends upon the preferential absorption by the fabric of the Lissolamine A and the consequent precipitation of the vulcanized latex. Fabrics were also made using an unvulcanized latex having superior fixative properties.

By impregnation in this manner, the carbon is confined to the body or core of the fabric so that a section of the fabric presents a laminated structure, the surface layers being clean and substantially free of carbon. The normal carbon content is 10–15 per cent.

Wearing trials of garments impregnated as above have been carried out by the British. The data obtained indicate the loss of protective value on wear to be due to (1) poisoning of the carbon through general soiling and perspiration, to which must be added any effect due to atmospheric contamination, and (2) loss of carbon from the garments due to wear and inadequate initial fixation. Of these, (1) is the more serious. The carbon exerts an abrasive action on the textile and increases the rate of wear. The effects of the carbon poisoning are reversed by extraction with acetone and presumably by other solvents. The impregnated fabrics show progressive loss of penetration times on standing in the atmosphere, presumably due to adsorption of atmospheric impurities of an oily nature. The fabrics also suffer deterioration of the fixation of the carbon on exposure to bright sunlight. A limited evaluation of carbon-impregnated garments was carried out by exposing subjects wearing new and worn "pantees" to H vapor, and it was demonstrated that the garments would provide a certain degree of protection.[28] However, due to the exploratory nature of this work, it is difficult to compare the results with the results of the chamber programs at Edgewood Arsenal and and the Naval Research Laboratory.

No work has been carried out in the United States on the use of rubber latex as a binder. Following the development of the above impregnation procedure, the British assigned a low priority to work on carbon protective clothing, presumably because of the unavailability of rubber latex and the deterioration of the activated carbon on wear and storage, with the result that practically no work was carried out after 1943.[29] It is believed that the British process is not so suitable for the impregnation of comparatively thin and tightly woven cotton fabrics as for the thicker woolen fabrics.

27.3.6 Impregnation of Piece Goods in Finishing Plant [1,2]

Certain alginic acid salts have the unique property of preventing activated carbon in a fabric from being inactivated by the application of a water emulsion of an acrylate polymer. This is used in the following modification of the British process for the impregnation of piece goods in the textile plant.

The processing of the fabric starts with the dyeing of the base fabric, since the darker shade of the fabric after the activated carbon has been incorporated makes it necessary to have the unimpregnated fabric a lighter and more yellow shade than the standard olive drab. Unmercerized cloth is used to secure better penetration of the carbon into the goods. Other than the above, the preparation of the base fabric involves the usual processing, namely, singe, diastafor, wash, 18-hour kier boil, sour, wash, wash, soap, hot water wash, frame-dry, dye.

The impregnating bath is prepared according to the following formula: 4 per cent ammonium alginate (Amoloid LV), 2.8 per cent zinc sulfate heptahydrate, 4 per cent concentrated ammonium hydroxide (28 per cent NH_3), 15 per cent National activated carbon, 74.2 per cent water. The alginate, carbon, and zinc sulfate are dispersed or dissolved in separate portions of the water. The ammonia is added to the zinc sulfate solution and stirred until the zinc hydroxide has dissolved, after which the carbon is added. The dyed fabric is impregnated by running it twice through a mangle equipped with one brass and one maple roll. The cloth is not dried between runs, but the face of the cloth is reversed. Following the impregnation, the cloth is frame-dried and then given eight passes through a specially built scrubbing machine to remove the surface carbon. The fabric is then dried and topped with a 5 per cent aqueous emulsion of a copolymer of ethyl acrylate and methyl acrylate (Rhoplex WC-9). Following this, the goods are frame-dried and cured, washed in a Rodney-Hunt washer in cold water for 15 minutes, frame-dried, again given four passes through the scrubbing machine, frame-dried, Sanforized, given four passes through the scrubber with 0.2 per cent Kalye-A (an inorganic detergent consisting of 75 per cent sodium metasilicate and 25 per cent tetrasodium pyrophosphate), four passes through the scrubber with cold water, and frame-dried.

The properties of the finished fabric, NDRC Carbon-Impregnated HBT, Type A (B-191), are as follows:

Tensile strength (Scott pendulum type — ASTM grab method)	
Warp	144 lb
Filling	92 lb
Tear resistance (Scott inclined plane tester — ASTM trapezoidal method)	
Warp	10.7 lb
Filling	6.1 lb
Air permeability (method of Schiefer and Hoyland)[21]	2 cu ft/sq ft/min
H resistance	
NDRC titrimeter method [4] (10 μg H in 10 ml air applied/min/cm² at 25°C)	
Capacity at 99% retention efficiency	500 μg/cm²
Capacity at 95% retention efficiency	1,050 μg/cm²
Capacity at 90% retention efficiency	1,200 μg/cm²
CWS penetration time [13] (Directive 162, Edgewood Arsenal test)	281 min
Flexibility	Stiffness increased about 30% over base fabric as measured on Gurley R.V. tester
Color	Olive drab shade
Carbon content	3 mg/cm²

Three large-scale mill runs, each of 1,000 yards or more, have been made. The material was somewhat more stiff than the carbon-coated fabric. Much of the material produced was of a darker shade than desirable. This was in part a result of the relatively inefficient experimental scrubber which was employed. With a properly designed scrubber, the quality of the material produced could be improved. N-44 carbon was used in all the plant runs rather than the more active N-182 carbon which became available later. Evaluation in the toxic chamber [17] at Edgewood in the summer of 1944 indicated the material to be as effective as the carbon-coated fabric containing approximately the same amount of N-44 carbon per square centimeter. Inasmuch as the chamber trials indicated little choice between the carbon-coated and the carbon-impregnated fabric, and the former was less stiff and did not require a scrubbing operation in its preparation, efforts were concentrated on having the carbon-coated fabric thoroughly evaluated.

An alternative plant impregnating process was developed based on the use of Kopan, an alkali-soluble zinc cellulose, as the dispersing agent, and 1,000 yards of herringbone twill were impregnated to demonstrate its feasibility on a plant scale. This material was not evaluated in chamber tests or wearing trials, but it is believed to be the equivalent of the process employing zinc ammonium alginate.[4]

In the development of the above systems, many other binders were investigated, but none appeared to be more satisfactory than those used in the two processes described above. These alternative binders included polymers of the methacrylate, acrylate, oil-modified alkyd, phenol-modified alkyd, rosin-modified alkyd, urea-formaldehyde modified alkyd, urea-formaldehyde, polybutene, and polyvinyl alcohol types; natural and synthetic gums; maizein, casein, and chrome gelatin; sodium silicate; metallic pectates and alginates; and hydroxyethylcellulose.

27.3.7 Impregnation with Carbon from Aqueous Ammonium Caseinate Dispersions [13]

Casein has been found to serve as a binder for the impregnation of fabrics with activated carbon. Unfortunately, casein easily dissolves in dilute alkaline solutions and, therefore, has little washfastness. In the following procedure, the casein is insolubilized by treatment with formaldehyde to increase the washfastness. The preferred formulation has the following composition: 24 parts N-182 activated carbon, 18 parts "Mapico lemon yellow" iron oxide pigment, 12 parts casein, 0.5 part Daxad (naphthalene formaldehyde sodium sulfonate), 1.3 parts concentrated ammonium hydroxide, 237 parts water, excess gaseous formaldehyde. After the dry ingredients are thoroughly mixed either in a beaker or ball mill, the water and ammonia are gradually added with stirring. The material to be impregnated is soaked in the mixture and the excess liquid removed by wringing. The fabric is then dried in a laundry drier. The impregnated fabrics or garments are cured by exposure to the vapors of formaldehyde for 12 hours. This is carried out by sealing approximately 20 pounds of dry impregnated garments in large paper sacks in the bottom of which approximately 150 ml of 40 per cent formaldehyde solution has been poured. After curing, the clothing is dried in a drier vented to the outside until the odor of formaldehyde is not objectionable. Coveralls impregnated in this manner are too stiff to be worn and are softened by laundering in a wash wheel at 160 F for 15 minutes in 0.2 per cent Kalye-A, followed by three 5-minute rinses at 160 F.

A similar procedure was investigated in small-scale equipment simulating an M-2 T of O impregnation plant. The curing step was carried out by introducing formaldehyde vapor into the drier during the drying operation. After preliminary trials, the method was discarded since it was believed the amount of clothing which could be treated by an M-2 T of O plant would be too small to be practical.

Garments impregnated by the laboratory pro-

cedure offer considerable resistance to H vapor as determined by the CWS procedure. The laundry resistance compares favorably with that of the carbon-coated fabric.

Small-scale wearing trials were carried out with garments during the development work. Because of the stiffness of the laboratory-impregnated garment and the belief that the plant process was not practical, an extensive program for wearing trials and chamber tests was never undertaken.

27.3.8 Present Status of Carbon Impregnation Systems

The process based on the use of ethylcellulose, dissolved in tetrachloroethane, as a dispersing and binding agent for activated carbon holds much promise for the impregnation of garments, but has not been demonstrated on a T of O plant scale. The impregnation of piece goods in the textile finishing plant by any of the methods yet tried is believed to be inferior to the application of the carbon by the coating process described in the next section.

27.4 PREPARATION OF CARBON-COATED FABRICS[7]

27.4.1 Introduction

Carbon-coated fabrics are prepared by applying a mixture of finely ground activated carbon, dispersed in a solution of viscose, to the fabric by a standard knife-blade coating technique. The viscose is converted into regenerated cellulose by treatment with sulfuric acid, and the fabric is then subjected to a series of washings and mechanical treatments to soften the fabric and to remove chemicals and loosely held carbon.

27.4.2 Preparation of Herringbone Twill Fabric Prior to Coating

Standard herringbone twill gray cloth woven according to Quartermaster specifications will have a filling tensile strength, determined by the "grab" method, between 150 psi and the specification minimum of 80 psi, depending on the spinning and weaving equipment used by the manufacturer.[12] The filling tensile strengths determined by the "strip" method will be slightly different but will also vary from sample to sample.[13] The nonuniformity of the material results from the fact that the amount of yarn which must be used to give the fabric a minimum weight of 8.5 oz sq yd is more than is required to meet the warp and filling minimum tensile strength requirements, and the manufacturer is given the option of placing the excess yarn in either the warp or the filling. Since the fabric must be napped prior to coating, and napping involves a preferential weakening of the filling threads, the gray fabric used should have a minimum filling tensile strength of 125 psi. The material is uniformly napped on the "back" surface of the fabric to such an extent that the filling strength is reduced approximately 55 per cent, providing this is not below 60 psi. Following the napping, the gray goods are submitted to the usual finishing process and finally dyed an olive drab shade in accordance with the Quartermaster specifications. All traces of soap or synthetic detergent must be completely removed by thorough rinsing.

27.4.3 Preparation of Carbon

The optimum particle size for the carbon to be used in the coating process is approximately 25 μ. Carbon of this particle size mixed with one-half its weight of an iron oxide yellow pigment and coated on the fabric has an olive drab shade.[13] Material of a smaller particle size requires larger amounts of yellow pigment to obtain an equivalent shade, and carbon of a coarser particle size is not bound so firmly to the fabric. National carbon can be ground to an average particle size of 25 μ by micropulverizing the 12 30 mesh material and air classifying the ground product. PCI carbon is too hard to be ground in this way; however, it should be possible to grind it satisfactorily to a similar average particle size by other means.

Anhydrous N-182 National activated carbon adsorbs water to such an extent that it partially dehydrates the cellulose xanthate solution and irreversibly coagulates it. This is avoided by previously mixing the carbon with one-half its weight of water and allowing the carbon-water mixture to stand for 3 days to assure uniform distribution of the water throughout the material.

27.4.4 Preparation of Viscose

The viscose is prepared in the usual way from cellulose, in the form of wood pulp, by the following series of steps.

A. Treatment of the cellulose with concentrated sodium hydroxide.
B. Aging of the alkali cellulose formed in Step A.
C. Treatment of the aged alkali cellulose with carbon disulfide.

D. Aging of the cellulose xanthate solution formed in (C) for several days until the right viscosity is obtained.

The alkali cellulose (Step B) is usually aged at 18 C for 52 hours. Longer aging decreases the viscosity of the final viscose solution. The aging of the final viscose solution (Step D) is usually carried out at 18 C for 80 hours. The viscosity of the solution increases with the time and temperature of aging. The final solution has the following physical and chemical properties:

Cellulose content	7.5%
Alkali content	6.6-6.75%
Viscosity	3,500–4,000 cps at 25 C

27.4.5 Preparation of Coating Mixture

The composition of the coating mixture is as follows:

Viscose	72.1%
Carbon humidified with 50% its weight of water	23.8%
Iron oxide yellow pigment	4.1%

The viscosity of the coating mixture is between 20,000 and 25,000 cps at 25 C. The coating mixture should be utilized within 6 hours following its initial production since its viscosity will remain reasonably constant during this period of time. It is essential that the viscosity be maintained within a relatively narrow range if the coating operation is to be kept under satisfactory control.

27.4.6 Coating and Processing of Herringbone Twill

The coating mixture is applied to the fabric by means of a coating machine. The essential parts of this machine are two nip rolls to apply the coating mixture and an adjustable knife blade to remove the excess. The bottom of the two nip rolls is partially immersed in a trough containing the coating mass and picks up the material and applies it to the napped side of the herringbone twill as the fabric passes between the two rolls. The coated fabric then passes over the adjustable knife blade, which removes the excess of the coating mixture. The coating film is partially dried by passing the fabric over steam-heated drums, after which the fabric is batched on a roll.

The cellulose xanthate in the viscose film is converted into regenerated cellulose by passing the fabric into a dilute sulfuric acid solution. This is followed by rinsing with water, neutralization of the remaining acid in the fabric by a dilute ammonia solution, and final rinsing. Following this, the fabric is washed in a 0.2 per cent Kalyc-A solution in rope form in a slack washer. The washing is followed by hot and cold rinses to remove any detergent remaining in the fabric. The fabric is then framed and dried. The coated film is further broken up by repeatedly passing the fabric over a button breaker (a series of rolls studded with metal projections) while the material is maintained under as much tension as possible without injuring the fabric. If necessary, the material may then be subjected to further washings, or vacuum-cleaned to remove loose carbon. The fabric is finally Sanforized to insure a maximum shrinkage of less than 2 per cent.

27.4.7 Cost and Production Capacity [18]

It was estimated in 1944 that the cost of producing the carbon-coated herringbone twill would be approximately as shown in Table 1.[18]

TABLE 1. Estimated cost of producing carbon-coated herringbone twill.

Item of cost	Approximate cost per finished yard
Grey goods (40)" 68x48 1.55 herringbone twill) including freight from Lindale, Ga., to Lewiston, Me.	28.40¢
Preparing, dyeing (Vat OD7 shade), and napping the fabric including freight from Lewiston, Me., to Sayleeville, R. I.	20.50¢
Carbon-coating treatment including Sanforizing but exclusive of the cost of the activated carbon	13.20¢
Total, exclusive of the cost of the activated carbon	62.10¢

A coating machine will coat 1,000–2,000 yards per hour, depending on the speed at which the machine is operated. The capacity of slack washers and acid fixing ranges is approximately 2,000 yards per hour. However, several button breakers would be required to process the material produced by one coating machine, since this is a slow operation.

27.4.8 Characteristics of Finished Fabric

The properties of the fabric are summarized in Table 2.

27.4.9 Present Status

Several 500-yard runs and one 5,000-yard run have been made. The data obtained indicate that the degree of control achieved in the smaller runs was satisfactory. There is less certainty concerning the larger size runs because of variations introduced during the

TABLE 2. Properties of finished fabric.

Fabric characteristics [7]	Mean value	Maximum value	Minimum value
1. Tensile strength (grab method, lb in.)			
a. Warp	160	....	144
b. Filling	85	....	60
2. Tear strength (trapezoid method, lb)			
a. Warp	8.7	....	6.9
b. Filling	7.6	....	5.6
3. Porosity (cu ft/min/sq ft)	8.1	....	4.5
4. Carbon content (mg cm²)			
a. Original	3.1	3.5	2.7
b. After washing and abrasion	2.1	...	1.6
5. Heapacity (μg cm²), NDRC titrimeter method [7]			
a. Original	2,200	....	1,700
b. After washing and abrasion	1,020	....	740
6. Stiffness (mean flexural rigidity) (mg/cm²)	1,100	1,400	....
7. Shrinkage (per cent)			
a. Warp	...	2.0	....
b. Filling	....	2.0	...
8. H resistance times (min), CWS Directive 162, Edgewood Arsenal results			
a. Unwashed	300	....	....
b. Washed and abraded	265	....	....

processing. It is believed improvements in the coated fabric will result if the heating of the fabric following the coating operation is reduced to a minimum. The best system would be to have the acid-fixing range directly attached to the coating machine and not to dry the fabric before regenerating with acid.

27.5 PREPARATION OF CARBON-RAYON FABRICS [3,4]

27.5.1 Introduction

Carbon-rayon yarn is prepared by dispersing finely ground activated carbon in a viscose solution and spinning the resulting dispersion by the methods used in the preparation of "high tenacity" viscose rayon yarn. The carbon-containing yarn is characterized by a low tensile strength and a high frictional value; accordingly, special techniques must be followed if it is to be woven or knit successfully.

27.5.2 Preparation of Carbon

The optimum size of the carbon to be used in the preparation of the carbon-rayon yarn is approximately 5 μ. Coarser material will clog the spinnerets, and finer material may be less active because an increasing percentage of the agglomerates of carbon in the yarn will be completely surrounded by an H-impermeable cellulose film. In the case of 5-μ carbon and filaments of 1.5-denier size, few of the carbon agglomerates are completely walled off. Most jut out through the filaments, thus opening up passageways for the diffusion of gases back into the carbon agglomerates.

The carbon is best ground by the "micronizing" process using steam as a carrier gas. This method has been found suitable for the grinding of the different types of carbon investigated, namely, National carbon types N-44 and N-182, and the PCC and Carlisle carbons. Unwhetherized carbon has been used in all cases.

27.5.3 Preparation of Yarn

The spinning solution is prepared in the same manner as for high-tenacity yarn. The N-182 5-μ carbon is incorporated and the resulting dispersion aged, filtered, and spun in the usual manner. In spinning, special precautions must be taken to wash all acid off the yarn as rapidly as possible. This is done by having water drips on the godet and on the spinning funnel through which the yarn must pass before entering the basket. Because of the second water drip, the basket must be perforated with holes to allow the escape of the wash water. Unfortunately, the yarn must be processed in the form of skeins. It has not been possible to process the yarn in cake form because of excessive shrinkage and consequent breaking of the weak yarn. Processing consists essentially of thoroughly washing with water and drying. No soaps or synthetic detergents are used.

The amounts of carbon used have been such that the yarns contained 20–45 per cent carbon. The strengths of such yarns are very low, namely, about 0.6 g denier compared with 2 g denier for cotton and ordinary rayon and 5 g denier for nylon and high-tenacity viscose yarn. The activity of the carbon drops off when less than 20 per cent is in the yarn, presumably because the carbon particles are completely surrounded by a regenerated cellulose film. The carbon exhibits 50–80 per cent of its original activity when present in the yarn in the higher concentrations. The most practical percentage must be determined by balancing ease of fabrication and durability on wear against the activity of the carbon. In the case of N-182 carbon, wear and chamber trials carried out shortly before the end of hostilities indicated the best balance would be achieved when the

yarn contained 25–28 per cent carbon.[24] The properties of yarn containing 30 per cent N-182 carbon are as follows:

Dry strength	0.6 g/denier
Wet strength	Practically zero g/denier
Extensibility	12–15%
Frictional value	Very high

27.5.4 Weaving of Fabric

In the preparation of woven fabrics, the carbon-rayon yarn was used exclusively in the filling because of the increased ease of fabrication and the anticipated better wearing qualities. Due to the low strength characteristics of the carbon-rayon yarn, it was necessary to incorporate supporting yarns in the filling to increase the dry and wet strengths of the fabric. This was accomplished in two different ways. In the early experiments, a box loom was employed, and alternate filling threads were of carbon-rayon and of cotton (Costa fabric [3]). A better method involves plying the carbon-rayon yarn with nylon prior to weaving. A double twill construction, which is not apparent to the uninitiated, enables a major portion of the carbon-rayon yarn to be sandwiched between the two twill layers and thereby increases the durability of the fabric to wear. The characteristics of the NDRC Carbon-Rayon Twill, Series 148, Type 176, were as follows:

Construction: Double 2x1 twill, 100 warp ends, 108 picks
Warp: 60/2 cotton dyed OD7
Filling: 32% CWS N-182 carbon yarn, 350 denier 200 filament. Plied with 30–10 nylon (undyed) 5 turns Z, then plied with 105–34 nylon (dyed OD7) 5 turns Z.
Carbon content: 6.0 mg/cm²
Physical characteristics:
Weight:[b] 10 oz/sq yd
Warp tensile strength:[b]
Dry 113 lb/in.
Wet 93 lb/in.
Filling tensile strength:[b]
Dry 115 lb/in.
Wet 106 lb/in.
Permeability:[b] 43 cu ft/sq ft/min at 0.5 in. water pressure.
Abrasion resistance: 8.0% loss in weight of fabric after 2,400 rubs in Wyzenbeek abrasion meter at 3 pounds pressure and 3 pounds tension.
Resistance to H vapor:[b]
CWS method (Directive 162, Edgewood Arsenal result):[b] 320 min
NDRC nitrimeter method[c] (30 μg H in 14 ml air applied/min/cm² at 25°C)
Capacity at 90°; retention efficiency: 1,500 μg/cm²
Capacity at 45°; retention efficiency: 2,100 μg/cm²
Capacity at 90°; retention efficiency: 2,500 μg/cm²

[b] Data obtained on Sample No. 148 of nearly identical construction.[18]

Five thousand yards of the above material were produced and evaluated by the Naval Research Laboratory in wear and chamber trials.[22–26] It is anticipated that a similarly constructed double twill fabric in which the filling yarn contains 25–28 per cent activated carbon and is plied twice with 70–23 nylon will be superior from the standpoint of number of chamber exposures protected against after severe wear.[24]

The weaving of the material is slower than the weaving of herringbone twill since the fabric has 116 picks/in. instead of 45–50, and the loom efficiency is not so high as in the weaving of a cotton fabric. However, the experience obtained in the preparation of the 6,000 yards indicated that commercial production is feasible. Following the weaving, the fabric is given a water rinse, Sanforized, and dried. Soaps must not be used, and synthetic detergents should be avoided. Figure 1 is a diagram of the textile construction.

A fabric similar to that described above can be woven using a carbon-rayon yarn prepared from a staple fiber cotton blend. Indications were obtained that garments prepared from such a fabric (Sample No. 155) [a] had superior wearing qualities.[23,25] Enough work has not been done to demonstrate the practicability of carrying out the necessary manufacturing operations on standard textile machinery. The fabric is somewhat heavier and not so flexible as the fabric prepared from continuous filament yarn. Garments prepared from fabrics (Samples 190 and 191) similar to the NDRC Carbon-Rayon Twill, Series 148, Type 176 but containing 34 per cent PCC activated carbon instead of 32 per cent N-182 activated carbon performed as well as the Type 176 garments in a wearing trial and chamber test supervised by the Naval Research Laboratory.[24,25] If confirmed by future work, this would demonstrate that PCC carbon can be substituted for the N-182 carbon without sacrifice. Laboratory evaluation indicates the fabrics carrying the PCC carbon to be inferior to those prepared from the N-182 carbon.

27.5.5 Preparation of Knit Fabrics

A heavy knit fabric can be prepared from carbon-rayon yarn by the use of a Tompkins knitting machine. The physical and textile characteristics of such a fabric are as follows:

Construction: 32% CWS N-182 carbon yarn 350 denier, 200 filament plied with 58–1 cotton, knit on Tompkins machine with one end carbon yarn and two ends 21–1

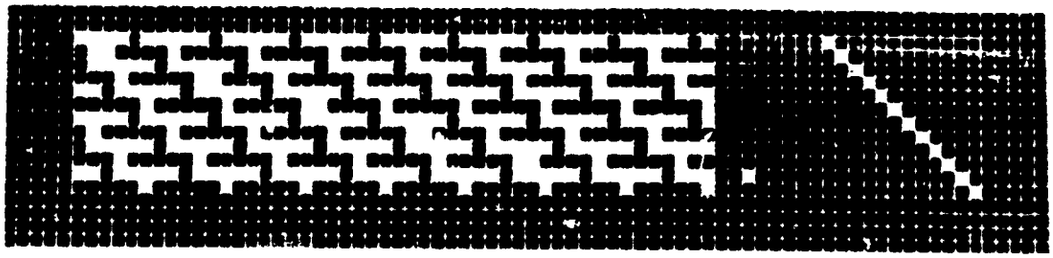


FIGURE 1. Diagram of textile construction of carbon-rayon double twill fabrics.

Diagram shows warp to be entered in harness comprising 12 shafts. Repeat of weave consists of 12 ends and 48 picks. Odd warp ends are used to provide covering of one side, even warp ends of other side of cloth. Filling is interwoven between 2 layers of warp ends, thus affording more room and protecting it against abrasion.[1]

cotton for the face and the same combination for the back.

Carbon content: Approximately 6 mg carbon/cm²
Weight unwashed: 15.3 oz/sq yd
Weight washed: 17.6 oz/sq yd
Resistance to H vapor: NDRC titrimeter method[4] (60 μg H in 32 ml air applied/min/cm² at 25°C)
Capacity at 98%; retention efficiency: 400 μg/cm²
Capacity at 90%; retention efficiency: 2,300 μg/cm²

NDRC Carbon-Rayon Knit Fabric Sample 180 corresponds to the above. It is believed that lighter fabrics involving the use of 200-denier carbon-rayon yarn and 30/1 cotton can also be knit commercially on a Tompkins machine, but this has not been satisfactorily demonstrated.

A large number of experiments have been carried out to make possible the use of other types of knitting machines. Due to the fraying and the frictional characteristics of the unlubricated carbon-rayon yarn, all these attempts have been unsuccessful. The Tompkins machine is unique in that it does not have sinker slots to become clogged. A large number of experiments have also been carried out to develop a successful lubricant for the yarn so that the other types of machines can be used. Laboratory data indicated the use of 10 per cent Carbowax on the yarn to be preferable to other lubricants; however, a knit fabric prepared from such yarn gave evidence of inadequately protecting subjects when worn in the form of shorts under chamber conditions.[4,17]

27.3.6 Use of Synthetic Fibers Other than Viscose Rayon

Synthetic fibers containing activated carbon have been prepared using various cellulose acetate compositions,[3] and various vinyl copolymers.[36] It was found in preliminary experiments that plain fabrics woven from the cellulose acetate yarns containing 10–15 per cent activated carbon appeared inferior when evaluated by the NDRC titrimeter method.[4] Two types of fabrics prepared from vinyon yarn[36] containing 25 per cent carbon performed very well in the NDRC titrimeter test.[4] One was an experimental hand-woven fabric with large carbon-vinyon yarns in both the warp and the filling. This fabric was prepared to simulate a filter cloth and was unsuitable for the preparation of garments. The other was a light-weight woven fabric prepared from cotton-vinyon staple fiber. A preliminary arm-chamber evaluation of this material at the Naval Research Laboratory indicated it to be slightly inferior to the carbon-coated fabric.[21] Since no facilities were available for the production of the material even if further work had created a demand, work on vinyon-carbon fabrics was discontinued.

27.3.7 Present Status

It has been demonstrated that woven fabric containing continuous filament carbon-rayon yarn can be produced using standard textile equipment. The material has a higher carbon content per unit area than other types of carbon fabrics and has a desirable "hand." Its protective properties after severe wear are superior to that of other carbon fabrics. However, its durability in wear is inferior to herringbone twill coated or impregnated with carbon, the increase in weight on wetting with water is greater, and the cost is estimated to be approximately twice that of the coated fabric. The thorough evaluation of the 6,000 yards of woven fabric should provide a basis for future decisions concerning the value of the material. The woven fabrics prepared from the carbon-rayon staple fiber and the knit fabric prepared from the

continuous filament yarn have not been produced on a large enough scale or evaluated thoroughly enough to enable a decision to be reached as to their value. The knit fabric would seem to have only limited usefulness in the preparation of underwear and socks because of its weight and textile construction, but it should be well suited for the preparation of gloves.

Cellulose acetate carbon yarns do not appear promising, but vinyon and other synthetic yarns containing carbon should be more thoroughly investigated.

Chapter 28

DETERIORATION, LAUNDERING, AND DECONTAMINATION OF CARBON-TREATED FABRICS

By *Homer Adkins* and *Wilkins Reeve*

28.1 INTRODUCTION

THE EXTENT of deterioration of carbon-treated protective fabrics has been studied under a variety of experimental conditions in order to assess better their probable protective value in the field. To be of practical value under field conditions, protective garments must not only provide a reasonable degree of protection when new but must retain an appreciable percentage of their original protective properties after being subjected to those conditions which will be encountered in practice, namely, storage, wear (including perspiration and soil), laundering, and decontamination. Carbon garments (by "carbon" or "chloramide" fabrics or garments is meant "carbon-treated" or "chloramide-treated" fabrics or garments) prepared by a variety of procedures are characterized by outstanding storage stability. They are partially inactivated by treatment with fuel oil or perspiration. Chapter 27 should be consulted for a description of the fabrics discussed in this chapter.

Methods of laundering and decontaminating carbon fabrics have been investigated and a practical procedure developed which both cleanses the garment and removes the major part of whatever adsorbed H [*bis*(β-chloroethyl) sulfide] is present. Ordinary soap cannot be used because it inactivates the carbon.

28.2 DETERIORATION ON STORAGE AND EXPOSURE TO ATMOSPHERE[4,7,15,16]

Samples of carbon-coated herringbone twill, carbon-impregnated herringbone twill, and carbon-rayon fabric have been subjected for several months to outdoor exposure and to simulated tropical storage.

In the outdoor exposure tests, samples were exposed from May to November on 45-degree angle racks facing south. Exposures were carried out in Washington, D.C., and in Florida. H penetration times were determined by the Naval Research Laboratory method (see Chapter 29) each month. The penetration times decreased during the first month except in the case of the carbon-rayon fabric (Table 1). After this initial decrease, the penetration times remained substantially unchanged during the succeeding months except in the case of the carbon-impregnated herringbone twill prepared by the zinc ammonium alginate process, which showed signs of failure after 4 months. This length of time under the exposure conditions employed is equivalent to a much longer period of wear than would ever be encountered in practice.

Storage tests have been carried out to determine the decrease in H resistance of carbon fabrics stored at room temperature and under simulated tropical storage conditions both alone and with chloramide-impregnated fabrics. When stored at room temperature, the chloramide fabrics have little effect on the H resistance of the carbon fabrics. Under simulated tropical storage conditions, the carbon-coated fabric stored with chloramide fabrics was adversely affected; the penetration time of the carbon-rayon fabric was not decreased on storage with aqueous-impregnated chloramide fabric, but the penetration time was halved after storage with solvent-impregnated chloramide fabric. The data are given in Table 2.

The deterioration of carbon fabrics prepared with

TABLE 1. H resistance times (NRL method) of carbon-treated fabrics after outdoor exposure.[7]

Exposure	Carbon-coated fabric (March model) (Wash.)	(Florida)	Carbon-rayon fabric (Cesta fabric) (Wash.)	(Florida)	Carbon-impregnated fabric (May model) (Wash.)
Original value	411 min		572 min		110 min
1 month	238	264	578	280	242
2 months	148	270	286	264	324
3 months	207	243	580	475	...
4 months	227	216	590	483	327
5 months	280	272	547	519	107
6 months	266	275	778	651	...

TABLE 2. H resistance times (NRL method) of carbon-treated fabrics stored with chloramide-treated cloths.[7]

Storage conditions	Penetration time (NRL method) carbon-coated fabric (March model)	carbon-rayon fabric (Costa fabric)
Original value	411 min	572 min
6 mo 110 F 75% RH	277 min	.....
6 mo 110 F 75% RH + solvent chloramide cloth	64 min	270 min
6 mo 110 F 75% RH + aqueous chloramide cloth	30 min	700 min
6 mo room temperature + solvent chloramide cloth	350 min	345 min
6 mo room temperature + aqueous chloramide cloth	336 min	429 min

rubber latex as a binder had been investigated earlier in the United Kingdom and found to be rapid under certain conditions.[16] To a certain extent, this was caused by the degradation of the binder and subsequent adsorption by the carbon of the decomposition products. On exposure to the atmosphere, the British fabrics suffered a loss of protective times, as measured by the Spotted Dick procedure, of such a magnitude that the penetration time of a fabric having an initial value of 140 minutes would decrease to 10 minutes after 6 weeks' exposure. It was shown that this loss was due to the adsorption of an atmospheric impurity rather than to a breakdown of the rubber latex binder, since fabrics containing no binder behaved in a similar manner. The activity could be completely restored by an acetone extraction unless the exposure had been at a temperature of 104 F or higher, in which case the fabric could not be revivified. Strong sunlight had a similar effect, but to a lesser degree. Penetration times of fabrics stored 2 weeks at a temperature of 104 F under moist conditions were reduced to 15 per cent of their original value and could not be restored by acetone extraction.

28.3 DETERIORATION DUE TO TREATMENT WITH VARIOUS SUBSTANCES

The resistance of carbon fabrics to H vapor, as determined in the laboratory, is not lost on treatment with a wide variety of water-soluble polar reagents, including such widely diverse compounds as low molecular weight alcohols (no appreciable effect),[2] cellulose xanthate (used in preparation of carbon-coated and carbon-rayon fabrics),[3] and solutions of hypochlorites (candidate decontaminants).[1]

Volatile solvents, such as gasoline and toluene, have little or no effect.[2,4] Only a limited number of chamber evaluations have been carried out to confirm the conclusions arrived at on the basis of the National Defense Research Committee [NDRC] titrimeter H resistance tests.[14] In the case of the Series 148 carbon-rayon fabrics, the number of standard chamber exposures for which subjects are protected against H vapor may be decreased from ten to seven following a mild laundering with Kalye-A (an inorganic detergent composed of 75 per cent sodium metasilicate and 25 per cent tetrasodium pyrophosphate), even though the laboratory test indicates but little change in the fabric.[1,14] After this initial decrease, the number of chamber exposures withstood by subjects is relatively constant regardless of whether the initial decrease is caused by washing the garments with 0.2 per cent Kalye-A, or by first subjecting the garments to a series of chamber exposures and then laundering with Kalye-A.[14]

Inactivation of the carbon may be due to either the preferential adsorption of another material or the mechanical coating of the activated carbon by an H-resistant film. In the first case, H adsorbed on the carbon may be desorbed, and further adsorption of H is prevented. In the second case, the carbon may still be active, but it is not possible for the H vapor to come in contact with it. The following sections list the substances known to inactivate the carbon.

Mineral Oil [9]

Chamber tests with human subjects have shown that carbon-rayon garments leak or desorb H vapor where fuel oil has been spilled. Rubbing H vapor-contaminated carbon-rayon garments with an oil-saturated rag causes the desorption of previously adsorbed H. Carbon garments contaminated with oil can be laundered with Kalye-A and restored to approximately their original activity. It is apparent that garments grossly contaminated with oil should not be worn. Traces of oil, such as would be obtained from handling rifles, are believed to be without effect.

S-330 Ointment [9]

It has been demonstrated in chamber tests that garments prepared from the carbon-rayon fabrics and worn in contact with S-330 ointment provide less protection than the carbon-rayon fabrics uncontaminated by S-330 ointment. It is believed that the triacetin vehicle of the ointment is preferentially adsorbed by the carbon.

Soap and Synthetic Detergents

Treatment of carbon fabrics with soap solutions

under the usual laundering conditions causes the adsorptive capacity of the carbon fabric to fall to one-third to one-half its original value.[2-4] The extent of the decrease depends on the presence of builders, the concentration of the soap, etc. The addition of certain compounds such as ammonium hydroxide and sodium phosphate lessens the loss in penetration time. Synthetic detergents such as Kalye-A, Nacconol NR (an alkyl naphthalene sulfonic acid sodium salt), and Triton 770 (sodium aryl alkyl polyether sulfate) caused much less loss in the penetration time than did soap.[1-4,7,14] Of these, Kalye-A is preferred.[2,14] Carbon-coated fabrics having an initial penetration time of 170 190 minutes unlaundered had a penetration time of 97 minutes after five launderings with a 0.2 per cent Kalye-A solution at 160 F; with a 0.5 per cent Triton 770 solution containing 0.25 per cent ammonium carbonate, the corresponding value was 45 minutes.[3]

Perspiration [10-14]

The rapid decrease in the protective properties of carbon-rayon and carbon-coated garments on wear is due in part to the loss of carbon, but mostly to the inactivation of the carbon by perspiration. Data obtained following the second Marine wearing trial at Camp Lejeune, North Carolina, in 1945 show that carbon-rayon garments (Type 176) after 2 weeks' wear provided adequate protection for two 1-hour exposures against H at a concentration of 10 μg l. New garments protect for an average of 4.5 exposures against 40 μg l. Carbon analyses on the same garments indicate that approximately 22 per cent of the carbon was lost during this period. Following this initial rapid decrease, the loss in the protective properties of the carbon-rayon garments during the subsequent part of the wearing trial was in proportion to the loss of carbon from the garment. In the case of the carbon-coated fabric, carbon analyses indicated one-half of the carbon to be lost after 4 weeks' wear. In the chamber, the garments protected for an average of 1.6 1-hour exposures against 5 μg l, whereas the new garments provided protection for six 1-hour exposures against 20 μg l. The data correlating the loss in protective properties as measured by chamber exposures and the loss of carbon for the carbon-coated (S 38 run) and the carbon-rayon twill (Series 176) are given in Table 3.

28.4 LAUNDERING AND DRY CLEANING OF CARBON-TREATED FABRICS

The preferred laundering procedure for all types of carbon fabrics involves treatment at approximately 150 F for a 15-minute period with 0.2–0.5 per cent Kalye-A followed by three 5-minute rinses with water.[2,3,14] The use of Kalye-A is recommended because, unlike soap, it has little effect on the adsorptive properties of the carbon as measured in the laboratory [3] and by chamber tests.[14] It is almost certain that the effectiveness of carbon garments as evaluated in a toxic gas chamber will be seriously impaired by one or more launderings with soap although there are no chamber data bearing on this point. Garments laundered with Kalye-A are effectively cleansed of dirt, oil, and resin, and, in addition, any H, HN1, or HN3 adsorbed on the carbon is nearly completely removed.[1-3,5,14] The tensile strength of the carbon fabrics is not materially lessened by the laundering treatment.[3] Nacconol NR has been used to launder carbon fabrics, but progressive loss of activity results.[4,7]

Early British work showed the Spotted Dick penetration times of their carbon fabrics to be relatively unaffected by low boiling candidate dry-cleaning solvents such as petroleum ether (bp 60 80 C), carbon tetrachloride (bp 77 C), or trichloroethylene (bp, 87 C). On the other hand, decaline (bp 190 C), and a petroleum fraction distilling around 180 C caused a major loss in penetration time.[17]

TABLE 3. Chamber tests with and carbon contents of worn carbon-treated garments.[10-13]

Fabric	New	Chamber exposures before break point 2 weeks' wear	4 weeks' wear	6 weeks' wear
NDRC Carbon-Rayon Twill, Type 148, Series 176				
NRL chamber exposures	4.5 exp. to 40 μg l	2 exp. to 10 μg l	2.2 exp. to 5 μg l	1 exp. to 5 μg l
% of original carbon content	100	78	53	25
NDRC Carbon-Coated Fabric, Run S 38				
NRL chamber exposures	6 exp. to 20 μg l	.....	1.6 exp. to 5 μg l	.....
% of original carbon content	100	.....	54	.....

Carbon-coated fabrics have had their H vapor penetration times reduced by over 50 per cent after being sprayed with a light machine oil or kerosene. After soaking the kerosene-contaminated fabric in tetrachloroethylene, toluene, or low molecular weight aliphatic alcohols, and air drying, the H penetration times were raised to more than their original values.[2,4]

Chamber tests have been carried out on carbon-coated garments which were exposed on subjects to H vapor until the suits failed to protect, laundered with Kalye-A (this treatment proved to be of relatively little value in this one case), and again exposed until the suits failed to protect. Soaking the garments in trichloroethylene reactivated the garments sufficiently so that subjects were protected for two exposures in the chamber compared with an original value of three.[6,7]

28.5 DECONTAMINATION OF CARBON-TREATED FABRICS

The removal of H from a carbon fabric by a 15-minute Kalye-A laundering has been shown to be most complete at a high temperature (175 F) with 0.5 per cent Kalye-A solution; if a lower temperature is employed, the concentration of Kalye-A should be increased.[1] Fabrics which were treated with five cycles of contamination with H vapor and decontamination with 0.5 per cent Kalye-A solution at 175 F have shown little loss in their ability to adsorb H as shown by retention efficiency measurements.[1] Chamber data indicate garments subjected to five cycles of a similar nature will protect subjects for 25–45 per cent of the time new garments will protect.[14] Garments were found to protect for approximately two-thirds the time of new garments when laundered once under the above conditions on a plant scale and worn by subjects exposed to H vapor under the usual chamber conditions.[14] Under plant conditions, the 175 F laundering causes excessive removal of the carbon from carbon-rayon fabrics.[1,5,14] For these reasons, laundering at 150 F is preferable.[14]

Other rapid methods for the decontamination of garments contaminated with the vapors of H, HN1, or HN3 include (1) boiling with water, (2) immersion in cold aqueous suspensions of a chloramide such as RH-195 containing sodium carbonate as a buffer, and (3) immersion in bleach slurries.[1] These treatments do not injure the tensile properties of the fabric, and may be of value for the decontamination of carbon clothing under emergency conditions in the field.[1]

Carbon garments contaminated with either H, HN1, or HN3 are self-decontaminating if stored for a few days under conditions of high humidity. In the case of HN1 and HN3, this process is quite rapid under Washington summer conditions. Even with H, however, storage at 80 F and 95 per cent relative humidity for 7 days causes the "active" H content of carbon-rayon fabrics containing 800 $\mu g/cm^2$ to decrease to 87 $\mu g/cm^2$. No pronounced loss of H, HN1, and HN3 occurs at relative humidities of less than 50 per cent.[8]

Chapter 29

LABORATORY EVALUATION OF PROBABLE PROTECTIVE VALUE OF FABRICS

By *Homer Adkins* and *Wilkins Reeve*

29.1 INTRODUCTION

THE REAL EFFECTIVENESS of a fabric in protecting a man against a vesicant can be ascertained only by men wearing garments made of the fabric, in a toxic atmosphere under realistic conditions. However, a laboratory method for comparing the probable protective value of fabrics is essential as a guide for research in the development and improvement of protective fabrics. The ultimate objective of this research is to produce fabrics that will protect men for a reasonable period against the concentrations of mustard gas (H) or other vesicants which are likely to be encountered in the field. However, the immediate objective is to develop fabrics which will withstand as long as possible the inevitable deterioration in the protective value of a fabric which occurs during storage, wear, and laundering, before it is called upon to protect the wearer. Many fabrics are sufficiently protective when first made, but this is not sufficient. An acceptable fabric is one that provides a reserve against deterioration in protective value.

A laboratory method for evaluating protective fabrics should make it possible to determine quickly and rather accurately the capacity of the fabric for detoxifying or adsorbing H. It should also indicate the efficiency or completeness with which the toxic agent is removed from an airstream passing through the fabric.

29.2 TEST PROCEDURES

The methods available from the Armed Services did not prove to be entirely satisfactory. The British Spotted Dick test was the simplest procedure available for estimating the protection afforded by permeable materials, and was used early in the cloth-testing program.[1,2] It is carried out by placing a drop of H in a small cavity beneath a sample of the material to be evaluated. The cloth is covered with a paper containing sodium carbonate, and this in turn is covered with an indicator paper consisting of Congo red paper spotted with a chloramide. Diffusion of H through the fabric and reaction with the chloramide on the test paper releases hydrogen chloride, which causes the appearance of a blue color on the test paper. The "protective time" is the time elapsing before the blue color develops. The procedure is rapid and no elaborate equipment is necessary. However, in the course of a considerable number of tests carried out under National Defense Research Committee [NDRC] contracts,[2,3] the method was found to have serious disadvantages. In particular, there is a very large day-to-day variation in the results obtained, and a quantitative measure of the amount of H detoxified or penetrating the fabric is not obtained.

In a test developed at the Naval Research Laboratory [NRL], air saturated with H at 30 C is kept in motion by a fan on one side of a fabric sample 16 sq cm in area. A current of clean air is passed over the other surface of the cloth at the rate of 200 ml/min, and carries the H diffusing through the sample into a bubbler containing 5 ml of 0.001*N* auric chloride solution. Each bubbler is equivalent to 0.6–0.9 mg of H, the end point being determined potentiometrically. The operation is repeated and, for successive measurements, concentration of H in the air current is plotted against time as measured from the beginning of the test. "Break time" for a sample is the period elapsing until the concentration of H in the air reaches 50 μg l. The humidity of air passing over the sample can be adjusted in the NRL procedure, and the concentration of H in the applied air can be readily varied.[4]

The NRL procedure was designed in the hope that it would correspond more closely to conditions encountered in actual warfare than the Chemical Warfare Service [CWS] dynamic test described below. In the latter, air is forced through the cloth, whereas it had been found that when air blows against cloth, as in a strong wind, only a very small proportion actually penetrates the material. However, the NRL procedure has disadvantages, perhaps the greatest of which is that there is no way of determining how much H has been actually applied or prevented from passing through the sample and, consequently, no

way of determining the efficiency and capacity of a protective material.

A later procedure developed at the NRL involves applying a measured amount of H vapor to one side of a permeable fabric and measuring the amount which diffuses through. The results of this test have been compared with chamber data; the bibliography should be consulted for a discussion of these data.[7]

In the CWS dynamic method, according to their Directive 162, air 80–85 per cent saturated with H, carrying 1.05–1.20, or, on the average, 1.13 mg/l, is passed through a sample of cloth at a rate of 200 ml of air per minute. Thus, on the average, 0.23 mg of H passes into the sample per minute. The area of the sample specified is 50 square centimeters, and, during the test, the whole apparatus is held at 30°C. The "protection" or "resistance time" is the period elapsing before 4.8 mg of H has penetrated the sample of fabric under test. This is the time required to decolorize three 10-ml portions of 0.001*N* potassium dichromate in 20 per cent sulfuric acid at 80°C. It is assumed that 1.6 mg of H is required for the decolorization of one bubbler holding 10 ml of the dichromate solution. The protection time is the sum of the times required to decolorize each 10-ml portion, less 22 minutes, the time required to decolorize the three portions when no sample is in the fabric holder.[8]

The CWS method makes it possible to assign to a fabric a single numerical value which, it was hoped, would indicate the protective value of the fabric when worn in an atmosphere containing H. The method was developed in response to a desire for a procedure whereby samples could be rapidly and routinely evaluated. The method suffers certain disadvantages. The area of the sample is such that it has not been feasible to obtain a uniform distribution of the airstream over the surface of the fabric. The method of determining the concentration of H in the airstream is rather reliable for air highly saturated with H, but the accuracy of the dichromate determination of H concentrations of 10–30 μg/l is not good. Experience has shown that it is not feasible to modify the method, as by changing the size of the sample, without getting into serious difficulty.

It seemed that the CWS dynamic test was sound in principle, but could be improved in several respects. Because the H is not uniformly distributed over the sample, the extent of reaction with H vapor in different portions of the sample differed with different protective agents. It is not possible, with the CWS dynamic method as described in Directive 162,[8] to determine the changes in retention efficiency with increased application of H to the fabric, and to differentiate clearly between the retention efficiency and the capacity of a fabric for detoxifying H. If dependence were placed on the CWS test, a low but adequate capacity in a fabric would sometimes obscure a high retention efficiency, whereas an unusually high capacity would sometimes obscure a dangerously low retention efficiency. Tests made by the CWS method indicated that S-461 was superior to CC-2 as an impregnite, although, in fact, S-461 is less effective than is CC-2.

It was felt that a sound test method would show the progressive change in the efficiency of the removal of H from the airstream by the fabric as the active agent was exhausted. The objective was to express the results in terms of the effectiveness of removing H from an airstream (retention efficiency) for the application of known amounts of H per unit area of fabric. The method which was ultimately adopted as embodying these characteristics utilized the Northrup titrimeter for ascertaining the retention efficiency and capacity of fabrics for detoxifying H.[9]

The reaction of bromine with H proceeds through formation of an addition product which decomposes slowly to form the sulfoxide:

$$(ClCH_2CH_2)_2S + Br_2 \longrightarrow (ClCH_2CH_2)_2SBr_2 \xrightarrow{H_2O} (ClCH_2CH_2)_2SO$$

In the Northrup titrimeter, H from an airstream is absorbed in a half cell containing 0.10*M* sulfuric acid in which is immersed a platinum electrode. This is connected to a standard half cell (silver electrode in 0.10 *M* silver nitrate) with a potential equal to that attained at the end point of the bromine-mustard titration. Since the addition of bromine to H is not a reversible oxidation-reduction reaction, no definite potential is set up in the titration cell, even in the presence of H, until an excess of bromine has been added. The burette remains open until the end point has been exceeded, when a large positive potential, depending on the Br^{-} Br_2 ratio, is set up. A current then flows through a galvanometer circuit, and the burette is closed either manually or automatically by means of a photoelectric cell and relay.[10,11] The preferred titrimeter was equipped with an automatic recording unit, which marked the opening and closing of the burette on a paper-covered drum revolving at a constant, known speed. The instrument gives an

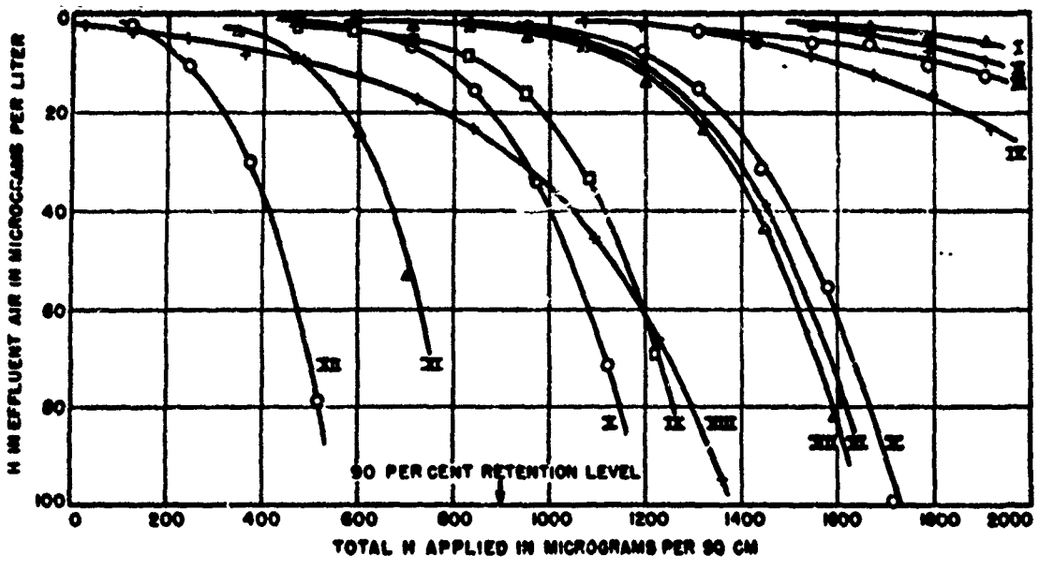


FIGURE 1. H concentration in effluent airstream versus total H applied to carbon fabrics. H in effluent air determined by Northrup titrimeter. Curves represent average of two sets of values except I, II, and III.

Conditions

Rate of H application: 10 μg min cm²
Rate of air application: 10 ml min cm²
Exposed area of sample: 7.5 cm²
Bromine concentration: 10^{-4} molar
Recorder setting: 6-min collections, 6-min titration
Basis of calculations: 85%; absorption of H in titration cell

Fabrics

No.	Type	Source, Designation	Carbon mg/cm²
I	Carbon-rayon twill	American Viscose, 118	5.0
II	Hand-woven "Amycon N"	Carbide and Carbon, 38-A	(25%; by weight)
III	Carbon-rayon, taffeta weave	Woonsocket Rayon, Costa 31003	6
IV	Carbon-rayon twill	American Viscose, 118-A	5.7
V	Carbon-impregnated HBT, Type B	Rohm and Haas, B-193	4.5
VI	Carbon-coated HBT	Kendall Mills, August Model No. 1	3.7
VII	Carbon-coated HBT, button broken	Kendall Mills, 8-31-2	3.1
VIII	Vinyon-cotton blend spun yarn fabric	Carbide and Carbon	2.8
IX	Carbon-coated HBT	Kendall Mills, October Model	3.7
X	Carbon-impregnated HBT, Type A	Rohm and Haas, B-191	3.6
XI	Carbon-rayon twill	American Viscose, 127	5.0
XII	Carbon-rayon twill	American Viscose, 110	4.3

accurate and almost continuous record of the concentration of H in the air which has passed through the fabric.

There are two objectives in setting up a testing method, which are somewhat incompatible with each other. One is to obtain a method by which a sample can be evaluated rapidly; the other is to test the fabric with air contaminated to the level which may be expected in the field. The most convenient concentration of H vapor for rapid determination is, as in the CWS method, 800–1,200 μg l of air, whereas a concentration of 10–50 μg l would be encountered in the field.[4]

There is little basis for a judgment as to the most realistic rate of application of H and air to the fabric, primarily because we do not know at what rate air passes through a garment worn by a man moving in air at various rates up to 20 mph. The average rate of flow through the fabric, according to the standard dynamic CWS test,[5] is only a few thousandths of a mile an hour. This may seem to be unrealistic, and it might seem that a soldier in the field would not

normally be in an atmosphere so nearly static. On the other hand, it well may be that the rate of air passage through a garment is of this order of magnitude, even when the individual is walking in a brisk wind. The actual rate of airflow through the sample, under CWS Directive 162,[4] is not known, since the rate varies at different points in the sample. If the distribution were uniform over the whole area of the sample, it would be 1 ml min cm^2 of fabric.

For the NDRC titrimeter method, two rates of airflow were ultimately chosen, i.e., 20 liters per hr or 44 ml/min/cm^2 (exposed area of cloth was 7.5 cm^2), and 4.5 liters per hr or 10 ml min cm^2. The rate of H application to a test sample was varied not only by a change in the airflow, but also by reducing the concentration of vesicant in the air at a given rate of airflow through the use of di-*n*-butyl phthalate to dilute the H in the saturator, as practiced at the Naval Research Laboratory. By a combination of these two devices, a wide range of application rates was available. Of these, the preferred rates were: an airflow of 20 liters per hr through pure H, which resulted in the application of 38 μg of H (0.038 mg) per minute to each square centimeter of cloth; or an air flow of 4.5 liters per hr through a solution of H in dibutyl phthalate, containing about 0.2 mole fraction of the former, which permitted the application to a sample of about 2 μg/min/cm^2. The first set of conditions, used for routine tests, was rapid and gave satisfactory results in the evaluation of materials which had capacities of 200-300 μg cm^2 and higher. The second set of conditions, in which the concentration of H is similar to that encountered in the field, was used in the testing of badly deteriorated fabrics, the H retentions of which were so low that no significant results could be obtained at a high rate of vesicant application. In addition, information was obtained about the retention efficiencies at very low H applications of materials of high capacity, although measurement of the capacities themselves was not practicable at so low an application rate, because of the time required.[1]

The results of the titrimeter method are best expressed in the form of a curve. The amount of H, applied to the sample in milligrams of H per square centimeter of fabric, is plotted against the concentration of H in the air which has passed through the sample. Values indicating the capacity of the fabric at any selected retention efficiency may be read from the curve and tabulated for ready comparison of fabrics. Typical data for various fabrics are given in Figure 1.[1] In this figure, the retention efficiency is equal to 100 minus one-tenth the micrograms of H in the effluent air.

If it be arbitrarily assumed that the capacity of a fabric is the amount absorbed before the concentration in the air passing through it exceeds 10 μg/l, then the fabrics referred to in the figure have capacities of about 200-2,000 μg/cm^2. During the application of most of the H, the concentration of H vapor in the effluent air was 2-3 μg/l. Thus 99.5 per cent or more of the H applied was being absorbed by the fabric.

Chapter 30

EVALUATION OF CHLORAMIDE- AND CARBON-TREATED FABRICS BY MEANS OF GAS CHAMBER TESTS AND FIELD WEARING TRIALS

By *Wilkins Reeve* and *Homer Adkins*

30.1 INTRODUCTION

THE ULTIMATE ASSESSMENT of the wearing qualities and protective properties of permeable protective fabrics can be made only by carefully planned and executed field trials. Field trials to determine the protective properties of garments necessarily lack precision because of the impossibility of setting up uniform concentrations of chemical warfare agents under field conditions. For this and other reasons, the degree and length of time of protection provided by garments against the vapors of H [*bis*(β-chloroethyl) sulfide], HN1 [ethyl-*bis*(β-chloroethyl)amine], and HN3 [*tris*(β-chloroethyl)amine] have been determined by exposing human subjects, wearing the garments to be tested, to the vapors of the chemical agent in toxic gas chambers under standardized conditions. The obtaining of accurate chamber data is time-consuming and requires careful experimental work, but the results are believed to represent a more reliable estimate of field performance than data obtained by presently used laboratory methods.

A series of field wearing trials have been carried out under a variety of climatic conditions to determine the suitability for field use of various types and combinations of permeable protective garments with respect to durability, comfort, and rate of loss or inactivation of protective agent; and to provide worn garments for chamber evaluation.

New protective garments of both the chloramide and activated-carbon types enable subjects to be exposed without harm to several times the lethal dose of H vapor. Chloramide* garments are inferior in protecting against the vapors of HN1 and HN3. Both types of garments deteriorate on wear at a rate such that the degree and time of protection may be inadequate after 1 week's wear under severe conditions. In general, the durability and wearability of protective garments are such that their use under field conditions is believed to be practical.

* By "chloramide" or "carbon" fabrics or garments is meant "chloramide-treated" or "carbon-treated" fabrics or garments.

All wearing trials and chamber trials in this country have been carried out under the supervision of the Armed Services. Because of the large numbers of men required and the legal and technical hazards involved, it has not been possible for civilian organizations to undertake this type of work. It follows that this chapter represents a review of the work carried out by the Chemical Warfare Service [CWS] and the Naval Research Laboratory [NRL] in this country, and by the corresponding organizations in Australia and India. With few exceptions, none of the data were obtained by National Defense Research Committee [NDRC] investigators.

30.2 GAS CHAMBER TESTS ON NEW PERMEABLE PROTECTIVE CLOTHING

30.2.1 Introduction

Tests in toxic gas chambers are carried out by exposing a group of six or eight men to an analytically determined concentration of the vapor of the chemical agent (usually 20–40 mg l) at a standard temperature (usually 90 F) and a standard relative humidity (usually 65–85 per cent) in a 20- to 50-m³ chamber. The men wear masks and are fully clothed in the protective clothing. Each man is exposed for 1 hour on either successive days or every other day until he shows an erythema or a more pronounced physiological reaction.[22,23] The men are exposed on successive days so as to approach the physiological end point with caution and also because it is not desirable to keep them in a toxic chamber for more than 1 hour at a time. Time must also be allowed after each chamber exposure for the lesions to develop. The relative protective values of different fabrics are estimated by determining the length of time during which the wearer does not suffer any pronounced physiological reaction.

Results obtained in man-chambers are different from results obtained using smaller chambers in which only a part of the body is exposed.[22,23,25] This is

due to several factors, one of which is the varying sensitivity of different areas of the body. Arm-chamber results are considered to be of value for screening fabrics prior to examination in a large chamber, but they do not serve as a substitute for results obtained in the latter.

In discussing the results of chamber evaluation, a distinction is made between the effectiveness of protection and the length of the period during which the garment will provide protection ("duration of protection"). All types of reasonably effective new permeable protective garments provide practically complete protection for at least 3 hours under the usual chamber conditions against H vapor, and some of them protect for several times this period.

Even under the best of circumstances, a certain small amount of the chemical agent can be expected to penetrate the permeable protective fabric. With CC-2 impregnated fabrics and H vapor, this leakage is sufficiently large so that the end point of the chamber test is due to the cumulative effect of the H which has penetrated the garment at each exposure. Only a small fraction of the CC-2 is used up, and a new subject wearing the exposed garment in an H atmosphere will be protected nearly as well as the original subject. The protection provided is due to the CC-2 reacting chemically with the H and converting it into practically nonvesicant chlorinated and oxidized products. With carbon fabrics, the protection provided is due to the adsorption of the H on the carbon. Small amounts of adsorbed H are held so tenaciously that no injury is produced even by prolonged close contact of the skin with the contaminated fabric. With larger amounts, the vapor pressure increases to such a point that a significant amount may migrate from the carbon to the skin, either by a vapor transfer mechanism or by first being extracted from the carbon by perspiration and transferred to the skin in the dissolved state. After this point is reached, the carbon fabrics provide relatively little protection and, if the fabric is not decontaminated, a new set of subjects wearing the clothing in an atmosphere free of H may develop a mild erythema from the loosely adsorbed H. The initial amount of H vapor penetrating a new carbon fabric is less than that penetrating a new CC-2 impregnated fabric. Accordingly, the end point of the chamber test is due to the activated carbon having adsorbed an amount of vesicant vapor such that a significant fraction is not firmly held.[47,48,54,60]

The capacity of carbon and CC-2 fabrics for adsorbing H from a saturated airstream in the laboratory is of the order of 1–2 mg cm² of fabric. Under chamber conditions, only 5–10 per cent of this capacity can be effectively utilized.[4,54,60]

The length of time for which subjects are protected depends on the number of layers of protective clothing worn, the temperature, wind velocity, relative humidity, extent of perspiration, and activity and previous history of the subjects, in addition to the many variables connected with the preparation of the clothing.[55] With subjects wearing untreated clothing, the severity of exposure under a given set of experimental conditions appears to be proportional to the concentration of the chemical agent multiplied by time of exposure. Available data suggest this relationship is also valid for subjects wearing carbon garments and exposed to H vapor,[54] but that the time of exposure is nearly independent of the H concentration in the range of 10–100 μg/l in the case of subjects wearing single-layer CC-2 clothing and exposed at 90 F and 65 per cent RH.[53]

30.2.2 Man-Chamber Tests with H Vapor

The results of chamber exposures at the Naval Research Laboratory and at Edgewood Arsenal [EA] are summarized in Table 1. The average number of exposures is given for which the first subjects wearing the test garments are protected. This corresponds to a "man break" rather than a "suit break" since the chemically impregnated garments would protect a second series of subjects for an approximately equal period of time.[53] Results obtained in two different chambers seldom agree precisely because of differences in the construction and operation of the chambers, the medical examinations of the subjects, and the general conduct of the tests. In the table, data obtained with one-layer clothing plus shorts are combined with data on one-layer-clothing alone, since the differences between the two are small. Most of the breaks occur on the back, which is protected in both tests by a single layer. In the latter case, scrotal burns also occur, although they often develop very slowly. No distinction is made between tests in which subjects were exposed every day and those in which exposures were every second day. If exposures were spaced sufficiently far apart, their effects would not be cumulative; in the data considered, however, it is probable that whatever differences exist are within the experimental error. The concentration of H was not kept constant in the Edgewood tests, and their published results give only the average Ct value

TABLE 1. Summarized man-break results of chamber evaluation of new CC-2 and carbon outergarments‡ with shorts against H vapor.

Garment	NRL data Number of 1-hour exposures 90 F, 65% RH	EA data Number of 1-hour exposures 90 F, 85% RH	Mg active chlorine or carbon (start of test) per cm²	NDRC titrimeter test§ (10 μg H in 10 ml air applied min. cm² at 25 C) Capacity (μg H cm²) at retention efficiency of 98%	90%
Untreated dungarees	1 (3 μg)[31]			0	0
CC-2 unstabilized (M-1) solvent process (100 CC-2, 75 CP/TCE solvent)	7.3 (20 μg)[35]	4.4 (30 μg)[26] 2.8 (48 μg)[27]	0.4	550 400*	950 1,300*
CC-2 stabilized (% of 1) solvent process Army: (100 CC-2/10 $CaCO_3$ 75 CP/TCE solvent)		3.9 (30 μg)[26]			
Navy: (100 CC-2/15 ZnO/75 CP/TCE solvent)	6.7 (20 μg)[34]		0.4		
CC-2 standard aqueous process (Field or M-2 T of O) Army. (100 CC-2, 10 ZnO 75 CP, 5 PVA)		4.8 (30 μg)[26]		1,000	1,000
Navy: (100 CC-2, 25 ZnO/75 CP, 3.75 PVA)	4.5 (20 μg)[34]	1.7 (18 μg)[27]	0.5	600*	1,500*
CC-2 aqueous system, $CaCO_3$ stabilized (100 CC-2 10 $CaCO_3$ 75 CP 5 PVA)		4.8 (30 μg)[26]	0.5	1,000 850*	1,200 1,000*
CC-2 aqueous system, low binder (100 CC-2 25 ZnO 25 CP/2.5 PVA)	6.1 (20 μg)[37]		0.5		
CC-2 aqueous Aresklene system (100 CC-2 25 CP 10 Aresklene)	10.6 (20 μg)[37]		0.5	700†	1,000†
CC-2 Foam Process (100 CC-2 10 ZnO 75 CP/25 Naccanol NR)	6.1 (20 μg)[42]	13 (25 μg)[30]	0.5		
Carbon-coated HBT (N-44 carbon, Aug. and Oct. models)	3 (20 μg)[47]	2.2 (30 μg)[32]	3.3	1,150	1,500
Carbon-coated HBT (N-182 carbon, Run 8-38)	6 (20 μg)[43]		3.0		2,200*,¶
Carbon-impregnated HBT, Type A (B-191) (N-44 carbon)		2.4 (30 μg)[25]	3.6	800	1,200
Carbon-rayon double twill, Types 110 and 127 (N-44 carbon)	5.3 (20 μg)[41]		5	400	650
Carbon-rayon double twill, Types 130 and 140 (N-44 carbon)		2.9 (48 μg)[32]	6		
Carbon-rayon double twill, Type 148 (N-182 carbon)	10+ (20 μg)[41] 4.5+ (40 μg)		5.7	1,900*	2,600*
Carbon-rayon double twill, Type 191 (PCC carbon)	4.4 (40 μg)[44]		5.7		‖
Carbon-impregnated garment (N-182 carbon, aqueous methylcellulose procedure)	3.7 (20 μg)[51]		3.8	>1,700*	>2,200*,¶

* Tested at four times given flow rate.

† Tested at four times given flow rate. Impregnation formula included $Ca(OH)_2$ stabilizer.

‡ Chapters 26 and 27 should be consulted for a more complete description of the various protective fabrics and for references to the original reports concerning their preparation.

§ Laboratory H resistance tests carried out at the CWS Development Laboratory at the Massachusetts Institute of Technology according to CWS Directive 102 show the 100 191 type fabrics to have break times of 296 347 minutes compared to 500 550 minutes for Type 148 fabrics.[49]

to cause a burn and the range of concentrations in the chamber. The average number of exposures given in the table has been calculated from the Ct value and the assumed average H concentration in the chamber. The maximum error of the NRL data is believed to be considerably less than 20 per cent in the case of most of the systems. With two or three exceptions, all have been examined several times, and the results are, therefore, based on a considerable amount of experimental work.

Preliminary Edgewood Arsenal chamber data indicate that two layers of clothing protect for nearly twice the period of time indicated for one layer plus shorts.[27] Naval Research Laboratory data with single

layer, single layer plus shorts, and single layer plus shorts and undershirt, all impregnated by the standard aqueous procedure (75 per cent chloroparaffin) indicate the number of exposures tolerated under the standard chamber conditions to be 3.8, 4.3, and 6.5.[58]

A series of chamber trials have been carried out with single-layer aqueous CC-2 impregnated garments plus shorts to assess the effect of certain variables which should be of importance under field conditions.[53,56,59] Within the range of 10–100 μg l, the duration of protection is relatively independent of the concentration of the H vapor.[53] At concentrations below 10 μg l, the duration of protection increases as the concentration of H decreases.[53] There are no similar data for subjects with two-layer protection, i.e., impregnated outergarments and long underwear. Limited data indicate the duration of protection to be constant irrespective of whether subjects receive their exposure in 1 day or in parts on successive days.[53] Previous contamination with H vapor has no significant effect on the duration of protection providing the active chlorine content of the garments has not been seriously lowered.[59] Suits wet with salt water during exposure protect for eight 1-hour successive exposures, whereas control suits and suits wet with salt water and dried protect for approximately four exposures.[59] Failure to restore the active chlorine content of impregnite-free areas subsequent to spot testing with the CWS impregnite testing kit, M-1, does not seriously affect the protective capacity of the clothing.[59] S-461 protective ointment is more effective than S-330 ointment in restoring the effective active chlorine content of the areas used in the test.[59] The effect of increasing the relative humidity is twofold, the reactivity of the impregnite for H vapor is increased, but the sensitivity of the skin is also increased.[55] Temperatures higher than 85 F cause large areas of the body to become markedly more susceptible to H vapor.[54] A relationship appears to exist between the sensitivity of the skin and activity of the sweat glands. Maximum duration of protection is obtained at high relative humidities and moderate temperatures.[55] The effect of wind velocity and the activity of the subjects is of lesser importance.[55]

Exposures on successive days for a total of 4 hours to 20 μg of H in the chamber followed by a total of 16 hours' wear results in the average active chlorine content of CC-2 impregnated suits dropping from 0.50 mg cm² to 0.46 mg cm². The decrease is the same for unstabilized solvent, zinc oxide stabilized solvent, and standard zinc oxide stabilized aqueous impregnated clothing. If garments are worn by a series of different subjects so that suit breaks, as distinguished from man breaks, are measured, solvent-impregnated garments withstand an average of 27 exposures, zinc oxide stabilized solvent-impregnated garments an average of 35 exposures, and standard zinc oxide stabilized aqueous suspension suits an average of 49 exposures. The total number of exposures withstood is in proportion to the initial active chlorine content. The amount of active chlorine lost for the different parts of a suit are in the following order: elbow (most lost), knee, back, shoulder, seat, crotch (least lost). The duration of protection against 20 μg of H vapor per liter is less than 1 hour when the average active chlorine contents of the suits have been reduced to the following points by repeated exposure to H vapor: unstabilized solvent, 0.07 mg cm²; zinc oxide stabilized solvent, 0.11 mg cm²; and zinc oxide stabilized standard aqueous, 0.25 mg cm². Failure of the garments was undoubtedly due in large part to certain critical areas having considerably less than the average amount of active chlorine per unit area.[56]

Carbon garments have not been evaluated so thoroughly as CC-2 garments under chamber conditions to determine the effect of the variables discussed above. Data obtained on the No. 148 series of carbon-rayon double twills indicate the duration of protection to be inversely proportional to the concentration of the H vapor.[61] Since it is known that the skin is less sensitive to H vapor under cool, nonsweating conditions, and the absorptive properties of carbon are enhanced by cool, dry conditions, it can be predicted that carbon fabrics will protect for longer periods of time under less severe chamber conditions.

A series of chamber tests have been carried out in Australia to evaluate chloramide-impregnated clothing. The data obtained are in general agreement with the data given above, except that preliminary evidence was obtained indicating the duration of protection to be inversely proportional to the H concentration under the chamber conditions employed (90 F and 65 per cent RH).[72] This result is in agreement with the limited Edgewood data,[25,27] but not with the extensive Naval Research Laboratory data.[53] Data were obtained indicating good agreement between the results of annulus trials and of chamber tests.[71,72]

The field testing of H munitions has been carried

out under experimental conditions such that man breaks of protective clothing due to H vapor have seldom been experienced. Only standard protective clothing has been used to protect the personnel involved. No data have been obtained which cast doubt on the value of the toxic chamber method of evaluating protective garments.

A review has been made of chamber and field data published prior to 1944.[22]

30.2.3 Man–Chamber Tests with HN1, HN3, and Other Agents

Available data indicate that all of the types of carbon fabrics listed in Table 1 provide excellent protection against HN1 and HN3 vapors. CC-2 garments provide virtually no protection against the vapor of HN1, but considerable protection against HN3 vapor.

Subjects wearing carbon-rayon twill (Series 110 and 127) garments with shorts prepared from a knit carbon-rayon fabric have been exposed for 1 hour on each of 5 successive days to 30 μg of HN1 vapor per liter at 90 F and 65 per cent RH. Erythema developed on the neck and back of the subjects.[66,67] Subjects wearing CC-2 garments could not be included in the same test since CC-2 garments do not offer suitable protection. Ten men dressed in single-layer zinc oxide stabilized standard aqueous clothing were given a single 1-hour exposure to 6.7 μg of HN1 vapor per liter at 90 F and 65 per cent RH. Four days later, 8 of the 10 men had crusted lesions on the scrotum as well as milder burns on other parts of the body. Similar results were obtained with subjects dressed in one layer plus impregnated shorts. Subjects dressed in plain unimpregnated clothing received burns of comparable severity when exposed for 1 hour to 5 μg l.[66,67]

Man-chamber tests at Edgewood Arsenal with HN3 vapor have shown two-layer CC-2 garments to provide adequate protection against a Ct of over 5,000. The earlier NRL data with HN1 have been confirmed. Carbon fabrics have been found to give superior protection against both HN1 and HN3 (unpublished CWS Medical Division data).

CC-2 garments afford no protection against the severe skin irritation caused by exposure to CK concentrations[69] of the order of 2,000–3,000 mg m^3.

30.2.4 Arm–Chamber Tests

A series of arm-chamber tests have been carried out with the vapors of H, HN1, HN3, and L (lewisite), with the object of developing preliminary information so that the program involving the use of the man-chamber could be planned more effectively. The results obtained are seldom in quantitative agreement with those obtained in the larger chambers, but are usually in qualitative agreement.

All carbon fabrics tested provide excellent protection against the vapors of HN1 and HN3.[50]

Untreated clothing provides ample protection against the vapors of L. No protective clothing is needed except under abnormally dry conditions.[52]

Most of the data obtained have been confirmed and extended by man-chamber tests; accordingly, they need not be reviewed.[66,51]

30.3 OTHER PHYSIOLOGICAL TESTS OF NEW PROTECTIVE FABRICS

Patch tests, drop and spray tests, and large-scale field tests involving the use of vesicants and human subjects have been used to evaluate the effectiveness of permeable protective fabrics against the important chemical warfare agents. Patch tests have been used to study the protective characteristics of carbon fabrics contaminated with H.[11,60] Large-scale spray tests have demonstrated that two-layer protective fabrics protect against fine droplets of H. Laboratory tests with drops of liquid H have been made to measure more accurately the degree of protection provided. The protection provided subjects wearing one- or two-layer protective clothing and traversing or occupying terrain contaminated with H in the liquid and vapor state has been assessed by field trials.

It has been demonstrated by spray tests that 90 per cent of the subjects wearing two layers of CC-2 clothing will be protected against low altitude unthickened H spray composed of 0.6- to 1.2-mm diameter drops at contamination densities up to 8 g m^2. Only 50 per cent of the subjects will be protected by a single outer layer of CC-2 clothing. More protection is afforded by a single layer of CC-2 clothing if it is worn beneath an untreated layer than when worn over an untreated garment.[23]

Protective fabrics have been evaluated in the laboratory against a fine mist of H droplets by determining the contamination density necessary to cause subjects wearing the fabrics to develop a physiological reaction. Drops of H weighing approximately 0.05 mg have been applied under room temperature laboratory conditions to single- and

double-layer CC-2 fabrics and to unimpregnated fabric. Approximately 1 g/m² penetrates two layers of unimpregnated fabric producing vesicles in 50

TABLE 2.[12] Penetration of single- and double-layer protective fabrics by H drops.

The cloth samples were attached to the forearms of human subjects and were removed 30 minutes after contamination with the doses of H listed below. The room temperature was 70 ± 5 F and the relative humidity 25 ± 6 per cent.

Fabric combination	Weight of H
Carbon-rayon twill (Sample 148)[18]	0.520 mg for 30% blisters
Carbon-rayon knit (Sample 182)[18]	0.260 mg for 30% blisters
Standard CC-2 solvent (TCE 20% $Ca(CO_3)$)	0.130 mg for 30% blisters
Standard CC-2 aqueous (20% $Ca(CO_3)$)	0.130 mg for 30% blisters
Standard CC-2 aqueous (10% ZnO)	0.130 mg for 30% blisters
Carbon-coated HBT (experimental plant run employing N-182 carbon) (S-35)[13]	0.065 mg for 30% blisters
Carbon-rayon twill (top) Carbon-rayon twill (underneath)	No skin reactions with amounts of H up to and including 4.6 mg
Carbon-rayon knit (top) Carbon-rayon knit (underneath)	4.6 mg for 10% erythema
Carbon-rayon twill (top) Carbon-rayon knit (underneath)	3.6 mg for 17% erythema
Carbon-coated HBT (top) Carbon-rayon knit (underneath)	4.1 mg for 41% erythema
Carbon-rayon twill (top) CC-2 aqueous (10% ZnO) underwear (underneath)	3.6 mg for 30% erythema
Carbon-rayon twill (top) CC-2 solvent (TCE 20% $Ca(CO_3)$ underwear (underneath)	3.6 mg for 75% erythema 4.1 mg for 100% erythema
Carbon-coated HBT (top) CC-2 aqueous (10% ZnO) underwear (underneath)	2.6 mg for 55% erythema 3.1 mg for 85% erythema
Carbon-coated HBT (top) CC-2 solvent (TCE 20% $Ca(CO_3)$ (underneath)	3.1 mg for 70% erythema 3.6 mg for 88% erythema 3.6 mg for 12% vesicles
CC-2 aqueous (10% ZnO) (top) CC-2 aqueous (10% ZnO) underwear (underneath)	4.1 mg for 47% vesicles
CC-2 aqueous (20% $Ca(CO_3)$ (top) CC-2 aqueous (20% $Ca(CO_3)$ underwear (underneath)	3.6 mg for 47% vesicles
CC-2 solvent (TCE 20% $Ca(CO_3)$ (top) CC-2 solvent (TCE 20% $Ca(CO_3)$ underwear (underneath)	3.6 mg for 67% vesicles

per cent or more of the subjects. Corresponding figures for single-layer and two-layer CC-2 clothing are 10 and 20 g m² respectively.[25-28] However, in a field test, erythema and vesicles were produced on some of the subjects wearing one-layer CC-2 clothing at contamination densities of 2 and 5 mg/m² respectively.[29] Wet clothing protects more effectively than dry clothing under these experimental conditions.[28]

Tests have also been carried out with a variety of fabrics with single drops (or multiple drops applied to one spot) of H to determine the maximum weight of drop against which the test fabric will protect.[12,27] In these tests, two layers of protective clothing were shown to be 20-30 times as effective as a single layer. The ratio is about 2 in tests with fine droplets, as discussed in the preceding paragraph.

H in droplets of approximately 0.006 mg (0.2 mm³) penetrates two-layer unimpregnated fabric more readily than similar sized drops of the liquid nitrogen mustards and is a better vesicant agent. With 43-mg drops (4 mm³) and two layers of CC-2 impregnated fabric, HN1 and HN3 do not cause such severe lesions as H, even though most of the H is destroyed by the impregnated fabric.[21]

Field tests have been carried out in this country, in Panama, and in Australia to determine the protection against H provided by CC-2 garments under practical field conditions. In a typical trial in Florida, the wooded terrain was contaminated with 50-150 g/m² by statically fired bombs. The temperature was 80-85 F. Patrols entered the contaminated area at various times and performed suitable maneuvers. If the maneuvers required the subjects to crawl on the ground within an hour or two after contamination, they were burned, even when clothed in two-layer CC-2 impregnated garments. Most of the burns occurred on the elbows and the knees. However, only erythemas resulted if the area was walk-traversed at this time by the subjects clothed in two-layer CC-2 impregnated garments. After 48 hours, subjects wearing unimpregnated outer garments and impregnated shorts could walk-traverse the area without hazard.[30] Trials at San Jose in Panama in tropical jungle, H-contaminated to 10-30 g/m² also indicate patrols can traverse the area 2 hours after contamination and that the resulting lesions will depend on the severity of the maneuvers. Subjects clothed in two-layer CC-2 garments can enter the area 2 hours after contamination and remain for 24 hours providing areas of visible liquid contamination are avoided.[31,32] Field trials in tropical jungle in Australia indicate troops clothed in two-layer CC-2 clothing can traverse terrain 24 hours after it has been contaminated with approximately 10 g/m². After 48 hours, the

terrain can be occupied by troops wearing two-layer CC-2 clothing.[71,72]

No field trials involving the use of chemical agents have been carried out with subjects wearing carbon clothing.

30.4 GAS CHAMBER TESTS ON WORN PERMEABLE PROTECTIVE CLOTHING

Several series of chamber trials have been carried out in this country and abroad to assess the protective properties of CC-2 and carbon garments which have been worn for 1 or more weeks in field wearing trials.[28,49,50,56,62,66,75] In Table 3, the results obtained with different types of protective garments in any one wearing trial are grouped together. Valid comparisons cannot be made between different types of garments worn in different wearing trials. Table 1 should be consulted for a more complete description of the garments.

Data on carbon-impregnated garments (methylcellulose procedure and casein-formaldehyde plant procedure) indicate a rapid decrease in duration of protection after 2 days' wear. Garments prepared from carbon-rayon staple fiber and from yarn containing 28 per cent N-182 carbon performed better than the Type 148.[66]

A field evaluation of CC-2 and carbon-coated herringbone twill was carried out at Camp Blanding, Florida, by the CWS during the summer of 1945. Data on this field trial have not been published; preliminary information indicates the duration of protection after 2 weeks' wear to be less than in the case of the Camp Lejeune data given in Table 3.

All data indicate a large drop in the duration of protection provided by garments which have been worn under hot humid conditions. The rate of loss of active chlorine is much less under temperate or cold weather conditions (consult Section 30.5.4), and the chamber performance after a given period of wear should be correspondingly better. Presumably, the same will be true of carbon clothing worn under conditions such that the subjects do not perspire excessively.

In the case of chloramide-impregnated clothing, the duration of protection for any one subject exposed in the chamber to H vapor is proportional to the chloramide content of the garment for any given impregnation process. This is true even though the chloramide present amounts to several times that theoretically needed to detoxify the H.[28,56] The relationship between the CC-2 content of worn garments and the duration of protection under chamber conditions is illustrated in Table 4.

The above data show no sudden change in the duration of protection provided by CC-2 garments

TABLE 3. Summarized man-break results of chamber evaluation of worn CC-2 and carbon outergarments with new shorts against H vapor.

Protective garments*	Wear	No. of chamber exposures at 90 F and 65% RH	
		New †	After wear
Panama,[49,56] March, 78 F and 78% RH mean day and night			
CC-2 ZnO stabilized solvent	6 days simulated combat wear	6.7 hr (20 μg)	1.2 hr (20 μg)
CC-2 standard aqueous process	6 days simulated combat wear	4.3 hr (20 μg)	1.7 hr (20 μg)
Camp Lejeune, N.C.,[50,56] August, 77 F and 72% RH mean daytime			
CC-2 standard aqueous process	1 day amphibious training 5 days field rifle practice	4.3 hr (20 μg)	1.2 hr (20 μg)
CC-2 aqueous system, low binder	5 days field rifle practice	6.1 hr (20 μg)	1.3+ hr (20 μg)
Camp Lejeune, N.C.,[61,66] July, 80 F and 80% RH mean daytime			
Carbon-rayon double twill, Type 148	2 weeks simulated combat	4.5 hr (40 μg)	2.0+ hr (10 μg)
	4 weeks simulated combat	4.5 hr (40 μg)	2.2 hr (5 μg)
	6 weeks simulated combat	4.5 hr (40 μg)	1 hr (5 μg)
Carbon-rayon double twill, Types 190-191 (PCC carbon)	4 weeks simulated combat	4.4 hr (40 μg)	1.8 hr (5 μg)
Carbon-coated HBT (N-182 carbon, Run 8-38)	4 weeks simulated combat	6 hr (20 μg)	1.6 hr (5 μg)
Australia,[75] May, 77 F and 75% RH mean daytime			
CC-2 unstabilized solvent M-1 process	2 weeks field exercises	>1.2 hr (15 μg)	>1.2 hr (15 μg)
CC-2 standard aqueous Navy M-2 process	2 weeks field exercises	>1.2 hr (15 μg)	>1.2 hr (15 μg)

* Table 1 should be consulted for a more complete description of the garments.
† Values taken from Table 1.

TABLE 4. Duration of protection against H vapor provided by worn CC-2 single-layer garments* plus shorts.

Garments	Active chlorine content	No. of 1-hour chamber exposures at 90 F and 65–85%; RH
CC-2 standard aqueous worn at Edgewood[75]	0.15 mg/cm²	1.7‡ (25 μg)
CC-2 stabilized solvent worn in Panama[19,56]	0.15 mg/cm²	1.2 (20 μg)
CC-2 stabilized solvent worn at Bainbridge, Md.†[56,63]	0.17 mg/cm²	1.8 (20 μg)
CC-2 unstabilized solvent worn at Bainbridge, Md.†[56,63]	0.17 mg/cm²	2.1 (20 μg)
CC-2 standard aqueous worn in North Carolina[56,58]	0.18 mg/cm²	1.2 (20 μg)
CC-2 standard aqueous worn in North Carolina[58]	0.23 mg/cm²	1.5 (20 μg)
CC-2 aqueous system, low binder, worn in North Carolina[56,58]	0.24 mg/cm²	1.0– (20 μg)
CC-2 aqueous system, low binder, worn in North Carolina[56,58]	0.28 mg/cm²	1.3– (20 μg)
CC-2 standard aqueous worn in North Carolina[58]	0.20 mg/cm²	2.1 (20 μg)
CC-2 standard aqueous worn in Edgewood[75]	0.3 mg/cm²	2.7‡ (25 μg)
CC-2 standard aqueous worn in Panama[19,56]	0.31 mg/cm²	1.8 (20 μg)

*Table 1 should be consulted for a more complete description of the garments. New garments contain approximately 10% CC-2 equivalent to 0.5 mg active chlorine per square centimeter.

†Chamber evaluation without shorts.

‡Data recalculated from original report.

as the active chlorine content is reduced. CC-2 aqueous impregnated garments protect for a somewhat shorter period of time than do CC-2 solvent impregnated garments of a similar low CC-2 content when tested under the standard NRL chamber conditions. Present practice calls for the reimpregnation of garments after the CC-2 content has fallen to one-third its initial value;[40] however, it is obvious that the need for reimpregnation is dependent upon the duration of protection which must be provided.

Only limited data are available concerning the duration of protection against H vapor provided by worn and reimpregnated CC-2 clothing under chamber conditions. In general, the number of chamber exposures for which subjects will be protected is dependent on the CC-2 content of the garments. A certain amount of chamber data are available, however, which indicates garments originally impregnated by the solvent system and reimpregnated by the aqueous system protect for a longer period than would be predicted on the basis of the active chlorine content.[56] CC-2 garments reimpregnated with an S-330 paste protect for a shorter period of time than would be expected on the basis of the active chlorine contents.[56]

30.5 TROOP WEARING TRIALS TO DETERMINE IRRITANCY, DURABILITY, AND RATE OF IMPREGNITE LOSS

30.5.1 Introduction

Most of the various types of permeable protective clothing have been worn in one or more troop wearing trials with the objective of obtaining reliable data concerning certain characteristics of the clothing which cannot be evaluated in the laboratory, namely, irritancy and comfort, durability, and rate of active agent loss on wear. In many cases, the worn clothing from the field wearing trials has been evaluated later against H vapor in a chamber; however, vesicants have not been used in the wearing trials themselves.

In a typical wearing trial, 5–10 different types of protective clothing may be evaluated by having groups of 10–30 men wear each type of clothing. The clothing is usually worn 24 hours a day for 6 days. On the seventh day, the subjects are allowed to bathe, the clothing is washed and dried, and the test resumed on the eighth day for another week, usually with the same subjects. The subjects are inspected daily for irritation; the clothing is inspected weekly for signs of wear and analyzed for impregnite content. The severity of the test will depend upon the weather conditions and the exact manner in which the test is conducted.

30.5.2 Irritancy of Permeable Protective Clothing

The irritation caused by the wearing of either impregnated or unimpregnated clothing is a function of the severity of the conditions under which the clothing is worn. Under temperate or cool weather conditions, clothing impregnated with CC-2 by any of the solvent or aqueous procedures will cause a negligible amount of irritation.[41,75] Under severe tropical conditions, whether or not irritation occurs will depend on such factors as the number of layers of impregnated clothing worn, amount of air circulation permitted by unbuttoning clothing during the daytime or while sleeping at night, frequency of bathing, frequency of laundering the clothing, duration of continuous wear, temperature and relative humidity at nighttime, and the procedure employed in the impregnation of the clothing.

In the following paragraphs, a brief review will be given of the results of the more important wearing trials carried out under hot humid weather conditions.

1. Panama, 1943.[42] Two-layer clothing impregnated with CC-2 by the standard aqueous procedure, CC-2 by the unstabilized solvent procedure, and S-461 by two aqueous procedures was worn day and night for six 6-day periods under severe conditions. Temperature and relative humidity averaged 80 F and 82 per cent. Clothing impregnated with CC-2 by the unstabilized solvent process was satisfactorily tolerated although it appeared to be slightly more irritant than unimpregnated clothing. Clothing impregnated with CC-2 by the standard aqueous procedure was more irritating, but still satisfactorily tolerated by a majority of the men. Clothing impregnated with S-461 caused incapacitating skin irritations after a few days.

2. Edgewood, 1943.[1,22] Two-layer clothing impregnated with CC-2 by a number of modifications of the standard solvent and aqueous procedures was worn day and night for 6-day periods. Temperature and relative humidity averaged 79 F and 71 per cent. The objective of the wearing trial was to serve as a guide for research on the development of less irritating aqueous impregnated clothing. Small numbers of men were employed so that a large number of systems could be evaluated; consequently, many of the differences observed are not statistically significant. CC-2 garments impregnated by the aqueous procedure were more irritating than those impregnated by the solvent procedure. Calcium carbonate stabilized aqueous CC-2 impregnated garments were less irritant than those prepared with zinc oxide as a stabilizer.

3. Panama, 1944.[32,49] Outergarments and shorts impregnated with CC-2 by the calcium carbonate stabilized aqueous and the unstabilized solvent procedures were worn by Army personnel under severe conditions day and night for two 6-day periods. Temperature and relative humidity averaged 80 F and 77 per cent. Both types of clothing were satisfactorily tolerated although the solvent impregnated clothing was the less irritant of the two. Marine personnel wore solvent and aqueous single-layer garments impregnated with CC-2 stabilized with 25 per cent zinc oxide, and unstabilized solvent impregnated garments. All were satisfactorily tolerated. Difference in irritation caused by the three types of garments were too small to be regarded as significant. The Navy protective clothing worn by the Marines is of a different design than the Army protective clothing (suspenders hold up the trousers, and there is no belt around the waist), a fact which accounts for the smaller degree of irritation observed.

4. Edgewood, 1944.[3,26] Two-layer clothing impregnated with CC-2 by a variety of aqueous and solvent procedures was worn by small groups of men day and night under severe conditions for two 6-day periods. Temperature and relative humidity averaged 76 F and 75 per cent. Additional data were obtained indicating calcium carbonate stabilized aqueous CC-2 impregnated clothing to be less irritant than corresponding zinc oxide stabilized clothing. The use of one-third the normal amount of chloroparaffin binder did not increase the irritancy to a measurable degree. Carbon-coated garments worn over unimpregnated underwear were substantially nonirritant.

5. Camp Lejeune, North Carolina, 1944.[30] Single-layer CC-2 impregnated garments and garments prepared from the carbon-rayon fabric were worn 12-15 hours per day under simulated combat conditions. Temperature and relative humidity averaged 79 F and 75 per cent. Less than 1 per cent of the men showed any signs of irritation.

6. Cannanore, South India, 1944.[30] Outergarments and shorts impregnated with CC-2 by the unstabilized solvent process and the zinc oxide stabilized aqueous process were worn 24 hours a day for periods up to 7 days under severe conditions. Temperature and relative humidity ranged from an average low of 76 F and 53 per cent to an average high of 94 F and 79 per cent. Of 76 observers wearing M-1 or M-2 impregnated outergarments, 5 per cent had significant generalized skin rash due to the CC-2 clothing, 69 per cent had mild, transient, insignificant rashes, and the remaining subjects were unaffected. None of the rashes required medical treatment, but it is considered that those listed as significant might have become troublesome if the subjects had been on active duty. A 7-day wearing trial of garments impregnated with 10-15 per cent CC-2 by the solvent process, and of garments impregnated with 4-7 per cent CC-2 by the aqueous process indicated little difference between the garments as far as irritancy was concerned. CC-2 impregnated garments were found to be nontoxic whereas subjects wearing AV impregnated garments rapidly developed severe toxic symptoms.

7. Finschhafen, New Guinea, 1945.[31] Outergarments and shorts impregnated with CC-2 by the

calcium carbonate and zinc oxide stabilized aqueous procedures, and the calcium carbonate stabilized solvent procedure were worn 24 hours a day for two 7-day periods. Subjects were permitted to bathe daily. Temperature and relative humidity averaged 81 F and 83 per cent. None of the types of clothing were very irritating.

8. Camp Blanding, Florida, 1945.[39] Two-layer CC-2 garments impregnated by the solvent and aqueous procedures were worn during a 2-week tactical exercise. Temperature and relative humidity averaged 83 F and 69 per cent. The performance of the troops wearing the clothing appeared to be as good as that of other troops wearing standard unimpregnated one-layer HBT fatigues. The men did not appear more exhausted, although they did seem to be more uncomfortable. A full report on this wearing trial has not been issued by the Technical Division, CWS, at the time of writing.

9. Camp Lejeune, North Carolina, 1945.[41] Single-layer CC-2 impregnated garments and several types of carbon garments were worn 24 hours a day for a series of 5-day periods under simulated combat conditions. Temperature and relative humidity averaged 80 F and 86 per cent. No increased number of skin irritations were observed in the case of those subjects wearing the protective clothing as contrasted with those not wearing protective clothing.

10. Proserpine, Australia, 1945.[76] Single-layer aqueous T of O CC-2 impregnated garments were worn 24 hours per day for 6 days and nights by paratroops in active training. Temperature and relative humidity in the afternoon averaged 85-90 F and 40-60 per cent. The subjects were allowed to bathe once a week. There were no signs of systemic intoxication or of chemical dermatitis, although some irritancy was observed which passed off with continuous wear.

Several wearing trials under tropical conditions with AV impregnated clothing have produced methemoglobinemia, cyanosis, and malaise.[68,70,78] It is to be noted, on the other hand, that all wearing trials with CC-2 impregnated clothing have confirmed its nontoxic properties.

A realistic field exercise involving the use of H has indicated that a high percentage of completely protected troops wearing masks and two-layer solvent impregnated CC-2 clothing under tropical conditions (80 F, 95 per cent RH) may develop a discomforting but not incapacitating dermatitis after 40 hours' wearing of wet impregnated clothing.[20]

The conclusion to be drawn from the data reviewed above appears to be that CC-2 impregnated clothing consisting of an outergarment alone or an outergarment plus shorts can be expected to be essentially nonirritant under hot and humid tropical conditions, regardless of the method of impregnation. Judgment must be more reserved in the case of two-layer garments, although the results obtained at Camp Blanding indicate they also should be sufficiently nonirritant for use under severe tropical conditions. Stabilized or unstabilized solvent impregnated clothing is undoubtedly less irritant than zinc oxide stabilized aqueous impregnated clothing. Calcium carbonate stabilized aqueous impregnated clothing is less irritant than corresponding clothing stabilized with zinc oxide. The last fact is of no importance in the wearing of clothing consisting of one layer or one layer plus shorts; whether or not the difference will be of practical significance in the case of two-layer protective clothing remains to be determined.

Carbon clothing is as nonirritant under hot humid conditions as untreated clothing of a similar weight and porosity. The only case on record of carbon clothing's causing irritation to the skin was with an early experimental run of the carbon-coated fabric. Unlaundered garments prepared from this material were worn by troops under hot dry conditions in a California desert and were found to be sufficiently stiff to irritate the skin. This is considered to be of no importance in view of the improvements since made in the textile characteristics of this material.[43]

30.5.3 Durability of Permeable Protective Clothing

All wearing trials have demonstrated the durability of zinc oxide or calcium carbonate stabilized CC-2 impregnated clothing to be equal or superior to unimpregnated clothing.[1,24,31,41,42,49] Clothing impregnated by the unstabilized solvent process may be slightly inferior to unimpregnated clothing; in any case, it does not differ greatly.[1]

A 1-month wearing trial under simulated combat conditions of garments prepared from carbon-coated herringbone twill indicates that they are as durable as untreated HBT garments.[41] Longer wearing trials have not been carried out. The durability of the various carbon-impregnated garments should be similar to that of garments prepared from the base fabric.

The durability of carbon-rayon garments depends

upon the details of the textile construction of the fabric. The results of a 2 6-week wearing trial under simulated combat conditions indicate increased durability results from double-plying the carbon-rayon yarn and having a yarn with as low a carbon content as other considerations permit. Fabric prepared from double-plied yarn containing 32 per cent carbon (Type 148, Series 176) showed practically no signs of wear for 2 3 weeks. Thereafter, the carbon-rayon threads frayed rapidly, and large areas of the garment were free of the carbon-rayon yarn after 4 weeks' wear. Garments prepared from fabric having a similar construction but containing 28 per cent carbon in the yarn were worn for 4 weeks, at which time they appeared similar to the above after 2 3 weeks' wear. After 6 weeks' wear, the 28 per cent carbon-rayon yarn had been completely removed from considerable areas of the garment. Garments prepared from carbon-rayon fabrics containing single-plied carbon-rayon filling yarn showed signs of wear after a shorter period than in the case of corresponding fabrics containing the double-plied yarn. Garments prepared from carbon-rayon staple fiber appear to be more durable than garments prepared from continuous filament yarn. Garments prepared from fabrics having 34 per cent PCI activated carbon in the filling yarn do not differ from the corresponding garments containing National carbon. All the carbon-rayon garments showing signs of wear had a striated appearance due to the nonuniformity of the carbon yarn. The differences between two adjacent areas of any given garment were more marked than the differences between different types of garments. Nonuniformity is believed to be inevitable with yarn produced on a small scale; yarn produced on a large plant scale should be of a higher quality and more uniform.[61]

30.5.4 Rate of Loss of CC-2 from Impregnated Fabrics

The loss of CC-2 from impregnated clothing on wear is caused primarily by the reaction of the impregnite with perspiration. The rate is dependent on the severity of the wearing trials, the method of impregnation, and the processing to which the base fabric was subjected prior to the impregnation of the garments with CC-2. Because of the probable chemical nonuniformity of the herringbone twill used in all wearing trials to date, all data on impregnated herringbone twill garments are subject to question. Data obtained with the Navy's CC-2 impregnated garments prepared from Arnzen cloth are considered to be more reliable from this standpoint since the Arnzen cloth is prepared by one company, is not processed extensively, and is not dyed.

Under mild winter conditions, the CC-2 content of outer garments originally impregnated by the unstabilized solvent procedure to 0.5 mg active chlorine per square centimeter (loading equivalent to 10 per cent CC-2) will have decreased to 0.15 mg active chlorine per square centimeter after 48 days' wear.[61] In the case of zinc oxide stabilized aqueous impregnated garments, the CC-2 content will have decreased to a similar extent after 30 days' wear.[6] As the temperature and relative humidity at which the wearing trials are carried out are increased, the rate of loss of impregnite increases. Under severe tropical conditions, two-thirds may be lost after 1-2 weeks' wear. Most of the field wearing trials, carried out under tropical or near-tropical conditions and described in Section 30.5.2, were carried out with the objective of determining the active chlorine content of the impregnated garments after given periods of wear, in addition to obtaining data on the irritation caused by the garments. A summary of the more important data obtained is given in Table 5.

The above data show that HBT garments impregnated with CC-2 by the solvent process consistently retain active chlorine for longer periods than garments impregnated by the aqueous process. Although the results of any one of the wearing trials is subject to question because the fabric quality is uncontrolled, it is doubtful if all of the data can be questioned on this basis.

An attempt has been made to simulate field wearing trials by having subjects wear patches of CC-2 impregnated fabrics strapped on the arm or sewn to the inside of their undershirts. Data obtained by these two types of patch tests are not always in agreement; furthermore, it has not been possible to demonstrate the superior characteristics of fabrics impregnated with CC-2 by the solvent system.[6,11] Both types of patch wearing trials indicated the processing which the base fabric received prior to impregnation to be of importance in determining the rate of loss of impregnite on wear. Fabrics given a severe processing treatment in the finishing plant retained active chlorine for a longer period of time than those given a light processing, even though both were impregnated under identical conditions.[7,8,11] Carefully controlled confirmatory full-scale wearing trials have not been carried out; however, a wearing trial in-

TABLE 5. Loss of CC-2 during troop wearing trials.[a]

Test and systems tested	% CC-2 retained: Outerwear	% CC-2 retained: Underwear[b]	Remarks
Panama, 1943 — 6 days' wear (HBT outerwear)[32]			
Unstabilized solution system	63	63	Large number of analyses averaged. Spread of 10% over garment area for aqueous, 20% for solution, with armpits and crotches lowest.
Aqueous system, 100 CC-2/10 ZnO/5 PVA/75 CP	53	54	
Edgewood, 1943 — 6 days' wear (HBT outerwear), average data from 6 wear periods[7,32]			No conclusions on CC-2 loss possible from this test. Very erratic results from week to week; weather not very severe.
Unstabilized solution system	80	73	
Aqueous system, 100 CC-2/10 ZnO/5 PVA/75 CP	68	74	
Panama, 1944 — 6 days' active wear, 1 day's rest (HBT outerwear)[32]			Very small number of samples; garments baled for 6 weeks after wear before titration. Data on underwear on one garment only.
Unstabilized solution system	50	90	
Aqueous system, 100 CC-2/10 $Ca(OCl)_2$/5 PVA/75 CP	35	21	
Panama, 1944 — 6 days' wear (Marines — Arnzen cloth)[19]			Data based on 6 analyses on each of from 5-11 Arnzen suits.
Unstabilized solution system	50		
Stabilized solution system, 100 CC-2/25 ZnO/75 CP	40		
Aqueous system, 100 CC-2/25 ZnO/3.75 PVA/75 CP	40		
Innisfail, Australia, 1944 — (HBT outerwear)[32]			Aqueous clothing loaded to 25% CC-2; solvent to 13%. Large number of analyses.
Unstabilized solution			
7 days' wear	76		
14 days' wear	58		
Aqueous system, 100 CC-2/10 ZnO/75 CP/5 PVA			
7 days' wear	51		
14 days' wear	32		
Edgewood, 1944 — 12 days' wear (HBT outerwear)[7,24]			Original CC-2 was 9-11% on all systems. Data based on analyses of 1-5 suits.
Aqueous system, 100 CC-2/20 $Ca(OCl)_2$/5 PVA/75 CP	30	37	
M-1 field set, 100 CC-2/10 ZnO/5 PVA/75 CP	18	13	
New Guinea — (HBT outerwear)			Large number of samples — 60 men; not under combat conditions.
Unstabilized solution system			
6 days' wear	71		
12 days' wear	56		
18 days' wear	25		
24 days' wear	10		
Camp Lejeune, North Carolina, 1944 — 16 hr per day for 8 days (Marines — Arnzen cloth)[20]			Garments worn during landing operations, followed by simulated combat tactics; Arnzen suits.
Aqueous system, 100 CC-2/25 ZnO/75 CP/3.75 PVA	33		
Aqueous system, 100 CC-2/25 ZnO/3.75 PVA/25 CP	35		
Flat goods impregnated in mill, aqueous system, 100 CC-2/25 ZnO/3.75 PVA/75 CP	20		
Finschhafen, New Guinea, 1945 — (HBT outerwear)[21]			Adequate sampling done, data probably most reliable of all tests.
$Ca(OCl)_2$ stabilized solution system			
7 days' wear	65	58	
14 days' wear including 1 laundering	37	33	
$Ca(OCl)_2$ stabilized solution system (outergarments and shorts)			
7 days' wear	55		
14 days' wear including 1 laundering	37		
Aqueous system, 100 CC-2/10 ZnO/75 CP/5 PVA			
7 days' wear	41		
14 days' wear including 1 laundering	9		
Aqueous system, 100 CC-2/10 $Ca(OCl)_2$/75 CP/5 PVA			
7 days' wear	42		
14 days' wear including 1 laundering	20		
Australia — (HBT outerwear)[18]			
10% ZnO 5 PVA, Aqueous			
6 days' wear including 1 laundering	70		
12 days' wear including 2 launderings	43		
18 days' wear including 3 launderings	23		
27 days' wear including 4 launderings	17		

[a] No impregnated underclothes or full-length drawers were worn in trials for which only outergarment data are given. Shorts were worn in most cases.

volving the use of extensively processed and lightly processed impregnated herringbone twill was carried out in Florida with the objective of determining how well certain types of gas protective equipment would hold up under simulated combat conditions. The few analyses which were made of the clothing were at irregular intervals; nevertheless, the data obtained indicate clothing thoroughly processed in the finishing plants lost its impregnite content at a slower rate than similarly impregnated garments prepared from lightly processed herringbone twill.[24]

Data obtained incidental to the chamber testing of CC-2 impregnated clothing indicate that much of the impregnite is lost during the wear following each chamber exposure rather than as a result of the action of the H vapor to which the subjects are exposed. It is of interest that garments impregnated by the zinc oxide stabilized solution system, the unstabilized solution system, and the zinc oxide stabilized aqueous system all lose an equal percentage of their original active chlorine content per unit of time. These data indicate the three types of impregnation to be similar in the loss of active chlorine due to exposure and wear.[58]

30.5.5 Miscellaneous Observations

Certain minor disadvantages attending the use of carbon clothing have been indicated by field wearing trials. Carbon-rayon garments are easily wet by water, and they dry out slowly. Consequently, the garments are heavy, and they easily pick up dirt. All types of carbon garments acquire a pronounced odor after wear under tropical conditions for several days. This odor appears to be caused by perspiration and is removed by laundering.[61]

Three realistic field exercises involving the use of H and two-layer protective clothing have been reported.[20,31,72] In Panama, completely protected troops wore masks and two-layer solvent-impregnated CC-2 clothing under tropical conditions (80 F, 95 per cent RH) and carried out simulated combat maneuvers over contaminated terrain. It was clearly indicated the troops had reduced endurance, alertness, and mobility; and their ability to use their weapons was impaired.[20]

Two-layer CC-2 impregnated clothing was used operationally during the invasion of France in the early summer of 1944. Only a brief report has been received; this indicates that the clothing was satisfactorily tolerated by the soldiers.[44]

30.5.6 Summary

Although the usefulness of protective clothing has not been demonstrated under combat conditions, an extensive series of laboratory and field tests with human subjects have shown CC-2 clothing impregnated by the solvent and aqueous procedures to provide excellent protection against H in the form of vapor and small drops. The various types of carbon clothing similarly provide excellent protection against all types of known vesicant chemical warfare agents. Available data indicate both types of protective garments can be expected to retain a reasonable degree of efficiency for 1–2 weeks when worn under severe tropical conditions, and for as long as 2 months when worn under cold weather conditions. Wearing trials have shown the clothing to be nontoxic and indicate that it is essentially nonirritant when worn under all except the most severe field conditions. Field trials indicate that troops wearing masks and protective clothing under field conditions will have reduced endurance, alertness, and mobility; and their ability to use their weapons will be impaired.

There is a need for accurate field data on the rate of loss of CC-2 from garments impregnated by the standard and certain experimental CC-2 formulations. Particular attention should be paid to the effect of mill processing received by the fabric prior to impregnation. Data are lacking on field and chamber performance of garments impregnated with activated carbon by the tetrachloroethane-ethylcellulose procedure.

Chapter 31

ANTIDOTES FOR POISONING BY ARSENICALS AND OTHER CHEMICAL WARFARE AGENTS

By *Homer Adkins* and *Wilkins Reeve*

31.1 INTRODUCTION

ARSENICAL WAR GASES, as exemplified by β-chlorovinyldichlorarsine (Lewisite) and ethyldichlorarsine (ED), function both as vesicants and as systemic poisons. Early in the war, British investigators discovered that 1,2-dimercaptopropanol and some other vicinal dithiols are effective antidotes for arsenical blister gases.[15-19] Compounds of this type were found to prevent vesication by Lewisite and to alleviate systemic poisoning by arsenic, if applied within an hour after exposure (see Chapter 7). Considerable attention has been devoted to the synthesis of vicinal dithiols and to the formulation and characterization of therapeutic compositions containing these agents.[12] Particular emphasis has been placed on 1,2-dimercaptopropanol (now known as BAL), in view of its outstanding effectiveness in combination with only moderate toxicity.

31.2 SYNTHESIS OF 1,2-DIMERCAPTOPROPANOL (BAL)

The method recommended by British investigators involves the reaction of 1,2-dibromopropanol, prepared from allyl alcohol, with sodium hydrosulfide in an appropriate solvent medium.[12,15-17] In initial National Defense Research Committee [NDRC] laboratory experiments, this procedure gave fair yields of the corresponding 1,2-dimercaptopropanol (BAL), but biological tests revealed the product to be slightly more toxic than a British sample employed as control.

After a detailed study of conditions for this synthesis, the procedure recommended for evaluation in semi-works equipment comprised the reaction of the dibromohydrin in methanol with sodium hydrosulfide at 60° C under hydrogen sulfide pressures in the neighborhood of 100 psi.[1] It was found most convenient to prepare the sodium hydrosulfide *in situ* from hydrogen sulfide and sodium hydroxide. This process was found to yield BAL of satisfactory quality from the standpoint of toxicity and chemical properties.

Precautions must be taken in the distillation of BAL, in order to avoid decomposition of the product. The most favorable procedure involves topping the reaction mixture to remove methanol, neutralization with hydrochloric acid, extraction of the BAL with chloroform, re-extraction of the chloroform solution with 10 per cent sodium hydroxide to remove 85-90 per cent of the BAL, and finally acidification and isolation of the BAL from the caustic solution. The alkali extraction procedure apparently removes impurities that favor decomposition of BAL at elevated temperatures. In addition, it was found that small amounts of ammonia or ammonium salts serve to stabilize BAL during distillation.[1] The above process was carried out successfully on a 10-pound scale and was adapted to commercial plant manufacture. A complete description of the processes is given in OSRD reports.[1,2]

31.3 BAL THERAPEUTIC COMPOSITIONS

With the successful production of BAL of acceptable quality from the standpoint of toxicity and chemical stability, the attention of a number of Office of Scientific Research and Development [OSRD] investigators was directed to therapeutic preparations, both for protection against and the treatment of lewisite poisoning. One of the first problems attacked was the formulation of a stable solution of BAL suitable for use in eye therapy. Attention was given to the chemical aspects of the problem, particularly in connection with the preparation of stable solutions of BAL in hydroxylated solvents suitable for use in the eye.[2] BAL proved to be quite unstable in aqueous solutions, but outstanding results were obtained with a 5.6 per cent solution of BAL in highly purified anhydrous ethylene glycol. It was found to be particularly important to keep the iron content of the solution to a minimum, preferably below one part per million, and to control the *p*H within limits from 4.5-5.3. The solution was adopted by the Medical Corps of the Army as the M-1 eye solution.

Investigation of BAL solutions in peanut oil, triacetin, and benzyl benzoate, has shown that a high degree of stability is realized in the absence of hydroxylated solvents. A preparation of 10 per cent BAL in 90 10 peanut oil benzyl benzoate has proved to be suitable for intramuscular injection and holds considerable promise in several clinical applications.[9]

Through the cooperation of representatives of the pharmaceutical industry, NDRC, and the Committee on Medical Research [CMR], 15 protective ointments containing BAL were prepared and carefully investigated from the standpoint of chemical stability and compatibility with BAL. As an outgrowth of this general program, a lanolin base ointment was adopted by the Navy, and a boric acid Carbowax ethylene glycol base ointment was tentatively selected by the Army.[4]

31.4 ANALOGS OF BAL

Concurrent with investigations of BAL, an exploratory study of chemical analogs was undertaken with the objective of uncovering materials superior to BAL in both therapeutic activity and toxicity properties. Approximately 60 analogs and derivatives of BAL containing a plurality of thiol groups were prepared and submitted for evaluation. Among these, 2,3-dimercaptopropyl ethyl ether proved to be outstanding for arsine therapy, although it exhibited toxicity for erythrocytes an action which is not characteristic of BAL itself.[12] In addition, a novel approach to compounds capable of liberating vicinal dithiols *in situ* was realized in *bis*-S-amidomethylthioethers of BAL, prepared from the dithiol, formaldehyde, and an appropriate amide. These compounds offered the advantage of lower initial toxicity, improved stability under tropical storage conditions, and lack of objectionable odor. Other products synthesized, which proved to have little therapeutic value in the biological tests carried out elsewhere, are derivatives of 2,3-dimercaptopropionic acid and condensation products of dithioglycerol with aromatic amines.

31.5 BAL GLUCOSIDE

About the middle of 1944, BAL glucoside, a new and apparently nontoxic derivative of BAL uncovered by British investigators, was brought to the attention of representatives of NDRC.[14] Because of its low toxicity, this agent was reported to be outstanding for use intravenously in combating systemic poisoning by arsenical war gases. Synthetic work on BAL glucoside was undertaken promptly with the aim of providing CWS and CMR investigators with materials for therapeutic evaluation. Initial attempts to duplicate the British preparation of BAL glucoside were carried out according to the following scheme:

$$\text{Glucose} \xrightarrow[\text{anhydride}]{\text{acetic}} \text{Pentaacetylglucose} \xrightarrow{\text{HBr}} \text{Acetobromoglucose} \xrightarrow[\text{Ag}_2\text{CO}_3]{\text{allyl alcohol}} \text{Allyl glucoside tetraacetate} \xrightarrow{\text{Br}_2} \text{2,3-Dibromopropyl glucoside tetraacetate} \xrightarrow{\text{K thioldiacetate}} \text{BAL-glucoside hexaacetate} \xrightarrow[\text{MeOH}]{\text{BaO}} \text{Barium BAL-glucoside}$$

For therapeutic use, BAL glucoside is liberated from the barium salt by treatment with 1 equiv of sodium acid sulfate.

The first product obtained proved to be low, both in thiol and total sulfur, although animal tests by medical investigators showed it to be considerably less toxic than BAL and highly effective for arsenic, cadmium, and mercury poisoning. More detailed studies led to improved products which were reported to be satisfactory from the standpoint of toxicity and activity following careful examination at the Medical Research Laboratory, Edgewood Arsenal. In general, BAL glucoside appears to be much safer than BAL for intravenous use because of its low lipoid solubility and ability to form stable, water-soluble complexes with metals such as arsenic, mercury, and cadmium. 1-Thiosorbitol, available from earlier NDRC work, was also found to be effective, although, in general, monothiols of this type are required in larger doses than dithiols to provide the same degree of protection against heavy metal poisoning.[15]

Since BAL glucoside is somewhat unstable and is prepared by a complex series of reactions, experimental work on the synthesis of simpler analogs was undertaken during the summer of 1945. It was hoped that stable vicinal dithiols solubilized by means of sorbitol or mannitol groups might be obtained by a simple series of reactions, but such compounds were not found before the end of the war.[16]

31.6 ANTIDOTES FOR MUSTARD

An extensive search has been made for antidotes for poisoning by H and the nitrogen mustards, but no compound has been found which is significantly effective. The lack of success in this search is probably due to the fact that H reacts rapidly and irreversibly with all the tissues of the body[6,7,11] (see Chapters 19 23).

Chapter 32

DECONTAMINATION

By *Jonathan W. Williams*

32.1 INTRODUCTION

DECONTAMINATION may be defined as the process of removing dangerous chemical agents or changing them into harmless substances.[27] The research undertaken in this subject during the war period has not resulted in any sweeping changes in the practices of the Armed Services. Nevertheless, real advances have been made in the accumulation of basic knowledge.

It was shown that techniques which are highly successful with mustard gas and lewisite are not necessarily applicable with nitrogen mustards and with certain lacrimators, such as bromobenzyl cyanide and chloroacetophenone. Special procedures have been developed for use with these agents.[7,17,21,22,47,52,55]

A search for new types of decontaminants has shown that for use with vesicants nothing compares in efficiency with the hypochlorites and the chloramides. A major portion of the effort in decontamination research has been devoted to the study of formulations of these active chlorine compounds which are superior to the bleach slurry and the solution of the chloramide, 1,3-dichloro-5,5-dimethylhydantoin (RH-195), in tetrachloroethane which are standard Armed Service items. An improved thickened bleach slurry was devised [19] and adopted by the Chemical Warfare Service. A chloramide dispersion system was developed [13,15,17] which is superior to the standard Army-Navy noncorrosive decontaminating agent (DANC; RH-195 TCE) in the following respects: it is less corrosive to metals and less injurious to painted surfaces, rubber, and plastics; it is made up of less toxic ingredients; it is effective, not only for H, L, and the nitrogen mustards, but for the lacrimators as well; and it is effective on a single application instead of requiring 3 or 4 applications.[17,24] The use of this material was not considered acceptable by the Services, however, because of objections to the time required for field mixing and the difficulty of removing the residual film left by the system.[52,53]

For the decontamination of protective clothing containing activated carbon, two procedures have been developed wherein the vesicant agent is satisfactorily removed without deactivating the carbon. These procedures are (1) laundering at 80°C using Kalyc-A, a modified sodium phosphate detergent, and (2) dipping in a cold aqueous suspension of RH-195 containing sodium carbonate.[18]

32.2 CHEMICALS FOR DECONTAMINATION

For the decontamination of vesicants such as H, L, or nitrogen mustards, no other classes of compounds have been found which react so rapidly and reduce the hazard so effectively as the hypochlorites and the chloramides. Tests have been made on at least [illegible] compounds of a wide variety of chemical types, without uncovering other substances capable of detoxifying vesicants rapidly.[2,11,14]

Although there are differences in the rates at which various chloramides react with H or with L, the rates of reaction of all chloramides tested are of the order of the reaction rate exhibited by bleaching powder with H, and therefore satisfactorily fast for decontamination purposes.[1,4,5,13] This situation does not prevail with the nitrogen mustards, which may be decontaminated with bleaching powder but not with all chloramides.[1,4,7,14] Chloramides which are particularly effective against nitrogen mustards include RH-195, S-300, S-126, S-136, and Decontaminant 40 (see Glossary for chemical names). A paste system described later and containing S-210 with potassium oleate has been shown to be effective against nitrogen mustards.[14,42]

Lacrimators such as CN and BBC are particularly resistant to the action of chloramide or hypochlorite systems. Special decontaminants have been devised for them.[55] The British used a saturated (0.25 per cent) solution of sodium thiosulfate in 78 per cent alcohol, and the United States Chemical Warfare Service standardized a 10 per cent solution of sodium hydroxide in a 10:26 mixture of water and carbitol. It has been shown that emulsion systems containing potassium oleate, such as the S-210 paste developed under NDRC auspices, are valuable in the decontamination of lacrimators.

32.3 FORMULATIONS FOR DECONTAMINATION

Vesicant agents such as H are readily absorbed and retained by paint and other organic surfaces; they present a difficult decontamination problem on naval vessels, aircraft, military vehicles, and other items of matériel. For such purposes, the Armed Forces adopted a decontaminating system called DANC and consisting of a solution of 1,3-dichloro-5,5-dimethylhydantoin (RH-195) in tetrachloroethane (TCE). Although this system decontaminates liquid H rapidly and is fairly effective for the decontamination of paint, it has serious disadvantages including injury to paint and plastics, corrosive action on bare metal surfaces, and high toxicity of the TCE. The National Defense Research Committee [NDRC] program has been directed toward the development of a fast-acting decontaminating system having the ideal properties of noninflammability, nontoxicity, noncorrosiveness, and noninjury to paint.

To be effective for the decontamination of paint, a chloramide decontaminating system must contain a solvent capable of penetrating the paint containing the absorbed vesicant. Systems in which the chloramides are in solution in the solvent medium (such as the RH-195 TCE system), as well as dispersion systems, have been examined. Significant improvements over RH-195 TCE have been obtained only with the latter type of composition.[10,13-15,17]

32.3.1 Chloramide Solution Systems

Solutions of chloramides offer potential advantages over dispersions in their simplicity and ease of handling. In attempts to find solution-type decontamination systems superior to the Armed Services' solution of RH-195 in TCE, a wide variety of solvent-chloramide combinations have been tried.[16] Tetrachloroethylene appears to be best of the solvents tested, in the light of essential requirements of low toxicity, noninflammability, and low injury to paint films, but it lacks solvent power for most chloramides and has low ability to penetrate paint. However, tetrachloroethylene has been used effectively in combination with other solvents which improve these properties. Mixtures with epichlorohydrin have been of particular interest, and solutions of RH-195 in tetrachloroethylene–epichlorohydrin mixture (70:30 by weight) appear equally as effective as RH-195 TCE for the decontamination of painted surfaces impregnated with H. Although no information on toxicity is available, it appears possible that this solvent combination is less toxic than TCE.

This work on chloramide solutions has indicated that all solutions of chloramides in solvents decontaminate paint relatively inefficiently, mainly because of the volatility of the solvent and the low concentrations of active agent which can be applied to surfaces by means of these very fluid solutions. The use of certain thickeners and waxes has been of value in reducing these defects but has the disadvantage of forming difficultly removable residues. Although numerous combinations have been tested, no solution systems have been found which are sufficiently improved over RH-195 TCE to deserve more detailed evaluation.[16]

Gradual loss of active chlorine occurs on storage of RH-195 TCE solution in brass decontaminating apparatus. The Army recommends replacement of this solution at intervals of 3 months. In a search for stabilizers, it was not possible to obtain complete inhibition of the decomposition in the presence of brass. However, small amounts of epichlorohydrin have been found to stabilize the solution against active chlorine loss in the presence of steel, suggesting consideration of the possible use of steel decontaminating equipment.[16]

32.3.2 Dispersion Systems

In the preferred system of those developed by the NDRC, the composition and proportion of ingredients which have been found to have optimum decontaminating efficiency are the following,[17] the quantities being expressed as parts by weight:

Tetrachloroethylene	67.3
Potassium oleate (containing 28 per cent water)	18.0
Barium hydroxide octahydrate (micropulverized)	2.8
Aristowax 160 163[c]	1.6
S 210 (micropulverized)	10.3
Appropriate camouflage pigments, if desired	(0.3)

This dispersion system has shown advantages over the solution of RH-195 in TCE, including lower toxicity of the tetrachloroeth*ylene* compared with tetrachloroeth*ane*, less corrosion of metals, and less injury to paints and plastics. It has the ability to decontaminate H, L, and nitrogen mustards in painted surfaces in a single spray application, in contrast to the 3–4 spray applications usually necessary with RH-195 TCE. The lacrimator CN, against which RH-195 TCE is not effective, is also readily decontaminated with this system. The time, manpower,

and amount of materials required for the use of the two systems are comparable. Outdoor evaluations have indicated satisfactory spraying properties for the dispersion system, and removal by washing with water is accomplished fairly easily in most cases.

In place of S-210, S-461 may be used in the potassium oleate/tetrachloroethylene dispersion system.[10] However, in spite of its higher active chlorine content, S-461 has not proved more effective than S-210 in the dispersion system. The instability of S-461 toward heating would result in danger on storage and shipment, and no satisfactory combustion inhibitor has been found.

The readily available chloramides RH-195 and CC-2 cannot be employed in the potassium oleate/tetrachloroethylene systems. Since these chloramides are stocked by the Army and Navy, special consideration has been given to the development of systems based on these as well as on other chloramides. Some promise has been indicated for a dispersion of RH-195 in a mixture of tetrachloroethylene and a white oil sodium sulfonate, but the results are generally less satisfactory than with the S-210 potassium oleate system described above.[14,15]

Under Navy auspices an emulsion paste system was developed which had certain advantages over the potassium oleate dispersion, particularly from the viewpoint of logistics.[42] It has the following composition:

Component	Parts by weight
Tetrachloroethylene	18
Emulsifying agent (either the monolaurate or monooleate of sorbitan, Span 20 or Span 80)	2
S-461 or S-210	7
Water (which need not be stored)	50

A comparison of this system with the potassium oleate S-210 paste and with the standard RH-195/TCE solution showed that the latter is the most efficient and the easiest to use in decontamination of H in Navy deck paint.[40-42] The factors considered in this study include rapidity of action, storage requirements, and the work involved in preparation and use.

32.4 SPECIAL STUDIES

Effect of H and of Decontamination Treatments on Airplane Fabrics

Work has been carried out to determine the extent of damage to fabric surfaces of combat airplanes which would result from war gas attack and from decontamination treatments.[9] At moderate concentrations (5 g/sq yd) of Levinstein H, neither temporary nor permanent injury to coated fabrics of the types used in Army and Navy aircraft resulted. However, the mustard penetrates the coatings and constitutes a definite hazard for several days under ordinary weather conditions. At high concentrations of H (15 g/sq yd) there is considerable initial loss of tautness of the fabric but recovery of satisfactory tautness occurs after overnight aeration. In decontaminating tests, the nitrocellulose-coated fabric used on military planes was decontaminated satisfactorily with the standard RH-195/TCE solution. However, this system caused serious loss of tautness of fabrics coated with the cellulose acetobutyrate lacquer used on Navy planes.

Estimation of Damage from a War Gas Attack on Factories

It was found that equipment typical of that present in factories tends to absorb and hold mustard, chiefly in crevices, paint, and oil, to such an extent that a severely mustardized factory would not be usable for a period of about 1 week in mild weather or a considerably longer time in cold weather.[8] The corrosion of metals by mustard gas, particularly in the presence of moisture, would be considerable although in most cases probably insufficient to prevent operation of the machinery. Decontamination by bleach-water slurries or by solutions of RH-195 or CC-2 in tetrachloroethane is effective but these agents are corrosive and clean-up after their use might be difficult. The use of the S-210/potassium oleate/tetrachloroethylene suspension described above would probably be advantageous in the event that decontamination more rapid than aeration is desired.

Decontamination of Carbon-Treated Fabrics

The NDRC has sponsored the development of protective fabrics carrying active carbon, which protect efficiently against vesicant gases (see Chapter 27). Work has also been carried out on the development of practical methods for the regeneration of these carbon-treated fabrics after a chemical warfare attack. It was desired to obtain decontamination methods which injure neither fabric strength nor the protective power against vesicants, and which require a minimum of time, labor, special chemical agents, and equipment. The effects of contamination and decontamination treatments on the protective powers of the fabrics have been estimated by tests of retention efficiency and by patch tests on rabbits.[18]

All conclusions resulting from this work are subject to further confirmation in chamber tests on human beings.

The effective decontaminating methods developed are classified as (1) washing techniques, suitable for use where laundering facilities are available, and (2) dip treatments, suitable for emergency first-line decontamination of carbon clothing.

Where laundering facilities are available, it has been shown that washing with dilute (0.5 per cent) aqueous Kalye-A solution at a higher temperature than usual (80 C) is effective in giving essentially complete decontamination of both carbon-coated and carbon-rayon fabrics.[18] Fabrics which have been treated with five cycles of contamination with H and decontamination with hot Kalye-A solution have shown no loss in ability to retain adsorbed H, as judged by vapor retention efficiency and animal tests. Fabric strength is not injured by this treatment. The relatively high laundering temperature is essential for complete decontamination. The use of Kalye-A appears particularly valuable because of its detergent powers; ordinary soaps and synthetic detergents are unsuited for use in laundering carbon-treated fabrics since they cause extensive lowering of the ability of the fabric to absorb and retain vesicants. Boiling water alone will effect fairly complete decontamination of H in carbon-treated fabrics without apparent injury to the fabric, but, of course, has no detergent value.

Where laundering facilities are not available, a "dip treatment" may be used. Carbon-treated fabrics contaminated with H are rapidly decontaminated by simple immersion in cold aqueous suspensions of RH-195 containing sodium carbonate as a buffer.[18] Biological and vapor retention efficiency tests have indicated that damage to the absorptive powers of fabric is relatively slight. Similarly, bleach slurries have given effective decontamination at low temperatures. These chloramide and bleach treatments have not appeared to injure the tensile properties of the fabrics. It is believed that these treatments should be valuable for decontamination of carbon-type protective clothing under emergency conditions in the field. They may also be used to advantage as pretreatments, to be followed by Kalye-A laundering as indicated in the preceding paragraph, in which case the laundering temperature may be 60 C or lower.

Nitrogen mustards adsorbed on carbon-treated fabric appear to decontaminate spontaneously and fairly rapidly on aging, but there is considerable damage to the adsorptive powers of the fabric particularly at high concentrations of nitrogen mustards.[18] Both the Kalye-A laundering and the chloramide or bleach treatments appear to be effective for the removal of the nitrogen mustard residues from the fabric and for giving good regeneration of its protective ability.

Thickening of Bleach Slurries

For general decontamination of vesicants, the Chemical Warfare Service has adopted the use of a 40/60 bleach/water slurry modified with sucrose as an antisetting agent. However, this slurry has been unsatisfactory because of its fluidity, which causes it to run off vertical surfaces. Division 9 developed a satisfactory method for thickening this 40/60 bleach/water slurry.[19] It was found that addition of 0.25 per cent micropulverized asbestos based on bleach, preferably used in conjunction with Duponol ME as a wetting assistant, causes thickening of the bleach slurry of the order desired.

Methods of Testing Thoroughness of Decontamination

In laboratory work it has been shown that there is only one truly satisfactory method of determining when a surface has been decontaminated sufficiently to be safe [12,24,26,44] for limited contact with human skin. This is the so-called patch test wherein a small panel cut from the surface being tested is worn in actual contact with human skin for a period of 30-60 minutes. The wearing period is followed by observations of the physiological effects.

Work in several laboratories has attempted to correlate the physiological testing with chemical methods of testing. One of the closer approximations has been worked out by the Chemical Warfare Service.[26] This method uses the DB-3 test for mustard gas and related compounds. Detector tubes containing silica gel impregnated with a DB-3 composition are exposed for a definite time to the area decontaminated, then heated and developed by the addition of sodium hydroxide solution. The intensity of the blue color developed is a semiquantitative indication of the amount of H vapor evolved during exposure. Color standards have been set up corresponding to "safe," "reasonably safe," and "unsafe," as determined by patch tests involving human skin tests with the same panel.

A similar scheme has been worked out by the Naval

Research Laboratory using test papers impregnated with a chloramide and Congo red.[44] An obvious limitation of these chemical tests is based on the fact that they measure only the vapor evolved from a surface, and hence do not provide a real evaluation of the danger inherent in contact exposure of long duration.

In one large-scale series of experiments utilizing 1,800 human volunteers, tests were carried out to correlate four methods of chemical detection of H in H-contaminated material with the irritancy of the material when applied to human skin for limited periods of time.[23] Twenty-one materials were used. The chemical methods were: (1) the chloramide-Congo red paper (Spotted Dick), (2) the DB-3 paper, (3) the DNB paper, and (4) the DB-3 cup test. None of the detector methods indicated at all readings what the skin reaction would be with every one of the materials. On the whole, the papers were somewhat better indicators of potential irritancy than the cup method. Of the papers, the Spotted Dick gave slightly more reliable results than the others.

PART V

DETECTION AND ANALYSIS OF CHEMICAL WARFARE AGENTS

Chapter 33

INTRODUCTION TO STUDIES ON DETECTION, IDENTIFICATION, ASSESSMENT, AND FIELD ANALYSIS OF CHEMICAL WARFARE AGENTS

By *Carl Niemann* [a]

THIS AND THE SIX following chapters deal with the work carried out in Division 9 (formerly Division B) of the National Defense Research Committee [NDRC] on the detection, identification, analysis, and field assessment of chemical warfare agents. The greater part of the work was carried out in Section 9.3 (formerly B3-B) and was guided by Service Directives CWS-6, CWS-14, NL-B25, NL-B32, NL-B33, NA-106, and AC-59.

It should be pointed out that the OSRD reports submitted by members of Section 9.3 do not represent the entire contribution made by the section relative to the above problems. In many instances it was necessary to work in close collaboration with the Armed Services, and in the interest of efficient and productive operation it was considered desirable to ignore organizational credit, particularly in respect to the NDRC. Thus many contributions made by section personnel are to be found in Service reports. This was particularly true in field work where, for purposes of morale and effective operation, it was imperative to remove the barrier between civilian and Service personnel, and the concession made by the NDRC in this direction indeed was small when compared with the results obtained at those installations where this attitude prevailed.

One can not avoid the conclusion that many of the section's activities were devoted to military problems which are now of historical interest only. In retrospect it appears reasonably certain that adequate methods were developed for the identification of the traditional chemical warfare agents and an account of this work is presented in Chapter 35. Of the miscellaneous problems presented to the section for solution it would appear from the account given in Chapter 39 that reasonable solutions were provided in practically all cases. The development of adequate methods for the field assessment of the persistent chemical warfare agents occupied much of the section's time and a description of this work is given in Chapters 36 to 38, inclusive. This activity was not only of value for the determination of munition requirements for the tactical use of persistent chemical warfare agents but also for the opportunity it gave for a realistic appraisal of the potentialities of traditional chemical warfare from the viewpoint of both offense and defense.

The determination of the presence or absence of a particular chemical warfare agent or a group of chemical warfare agents is not too difficult a task and many of the detectors described in Chapter 34 are suitable for this purpose. It should be pointed out that there is some question whether a chemical detector is really required for the detection of the common chemical warfare agents with the exception of the mustards (Chapters 5 and 6) and the newly developed Trilons (Chapter 9), because all of the others betray their presence in sublethal concentrations by characteristic odors or by their irritating qualities.

If a chemical warfare agent is present it becomes important to know the degree of hazard created by its presence. There is a tradition that the degree of hazard can be expressed as the product of the integrated concentration and the time of exposure, i.e., the dosage (Ct). It is well known that under field conditions absolute instantaneous concentrations vary greatly with time particularly when the absolute concentration is low. It is too much to expect that an observer will be able to obtain a reliable integrated value by making a series of determinations of the instantaneous concentration at arbitrary time intervals. What is required for the observer is an instrument capable of integrating successive instantaneous concentrations over selected time intervals and indicating the answer at any one time. Such an instrument is described in Chapter 38 and although this particular instrument does not satisfy the physical requirements of a device to be used in forward areas, it does suggest the principles to be followed.

[a] The author is indebted to Dr. Morris Jacobs for the preparation of a preliminary draft of manuscript. He is also indebted to Prof. E. H. Swift and to Messrs. Edward Bennett, David Brown, and George Holzman, all of the California Institute of Technology, for their assistance during the preparation of the final manuscript.

If the errors introduced by the assumption that the degree of hazard is independent of the magnitude of the absolute concentration prove too large to be ignored, and this is very likely, it will then be necessary to develop an instrument that will recognize and take into account the phenomena of threshold concentration arising from detoxification and reventilation processes. Such an instrument can and must be developed if a satisfactory device for determining the degree of vapor hazard arising from chemical warfare agents is to be obtained. To continue the practice of ignoring the basic problem because of the desire to have a simple if not primitive device certainly can not be productive.

With an instrument such as that indicated above at hand it should be emphasized that information will be obtained in respect to the degree of vapor hazard prevailing at the point or points of observation. To evaluate the degree of vapor hazard obtaining over an area not only requires observation of the degree of vapor hazard prevailing at a number of points but also proper evaluation of the meteorological and topographical factors. There has been an unfortunate tendency to associate micrometeorology with offensive tactics only, whereas it is probably of much greater value in devising suitable defensive measures because one can take observations on the spot and no remote forecasting is required.

The determination of the degree of hazard arising from the presence of liquid chemical warfare agents is discussed in Chapter 34. Few if any general conclusions can be drawn because the degree of liquid hazard is so intimately associated with topographical and climatological factors which can vary greatly between wide limits. It would appear, however, that this hazard in the past has been greatly overemphasized.

In the following chapters a serious attempt has been made to discuss the section's activities in as comprehensive manner as possible, whereas contributions made by other organizations and individuals are discussed only in so far as information in regard to their activities was available to the author. Because of the varying quality of liaison there is little doubt that many contributions, particularly those made abroad, escaped attention.

Chapter 31

DETECTION OF CERTAIN CHEMICAL WARFARE AGENTS

By *Carl Niemann*

31.1 INTRODUCTION

For the sake of discussion a distinction is drawn between detection and identification processes. It is considered that detection implies the determination of the presence or absence of a particular substance, whereas identification is the more general process wherein no or rather broad limits are imposed in regard to the nature of the substance to be characterized. Following there is discussed, first, the general nature of the tests proposed for the detection of certain chemical warfare agents and subsequently, their application as practical detectors.

31.2 SPECIFIC TESTS FOR DETECTION OF CERTAIN CHEMICAL WARFARE AGENTS

To be useful for the detection of a particular chemical warfare agent a test must be (1) specific, to insure reliability, (2) sensitive, to be useful, and (3) practical, to permit its use under field conditions. Since there are few if any simple tests that will differentiate homologs, in practice a test is considered to have adequate specificity if it will provide for the unambiguous recognition of a particular family of homologs or a group of compounds, each member of which contains the same functional groups.

31.2.1 Detection of Mustard Gas

One of the most significant problems facing investigators before and immediately after the outbreak of hostilities was the development of specific tests for mustard gas for field use in the event of employment of chemical warfare agents. To be sure, there were a number of tests described in the literature, the principal ones being the sodium iodoplatinate test, the gold chloride test,[123] Grignard's test,[124] the β-napthol test,[125] and the selenious acid test.[126] These tests were not sufficiently specific for mustard gas and were also inadequate from the point of view of sensitivity. There were other tests of even more dubious value described in the literature.[127,128] In a Chemical Warfare Service study in 1928,[74] five types of reactions were considered for the detection of mustard gas. The most useful tests were the indophenol blue, silver nitrate, Grignard's sodium iodide, sodium nitroprusside, and auric chloride tests. To this, perhaps, might be added the quinone dichlorimide and mercuric nitrate test for special use in the detection of liquid mustard gas. The sodium iodide test for the detection of mustard vapor, even in the absence of any possible interference, was inadequate because of its lack of sensitivity. No conclusion was reached in the study cited as to which of the above was the best all-round test. None possessed all the desirable properties of high specificity and sensitivity and simplicity of operation. The sodium nitroprusside test was most frequently used in experimental work on the destruction of mustard gas. Grignard's sodium iodide reagent or the modified reagent was found to be best suited to the detection of mustard gas in contaminated soil. In the testing of the atmosphere for mustard vapor, the use of an absorbing bubbler proved to be best. The detection of mustard vapor with impregnated test papers was not developed to a practical stage.

DB-3 Reagent. During 1941 a new reagent was found which offered particular promise for the detection of mustard gas.[2] This reagent was 4-(*p*-nitrobenzyl)-pyridine (DB-3). This substance will react with any compound containing an alkylating functional group to give a pyridinium compound which can be converted to a highly colored basic form by the addition of alkali. There is a very close analogy between the above reaction and the formation of the cyanine dyestuffs. Since mustard gas is an excellent alkylating agent, its reaction with DB-3 is readily understood. The reaction of DB-3 with a great variety of compounds has been studied,[22] and at present the behavior of this reagent toward different types of compounds can be accurately predicted. Other pyridine derivatives were found to be as sensitive as DB-3 but were either unstable or developed colors which were less intense than that of DB-3.[24c,f,a,b] Because of the importance of this reagent and its scarcity, it was necessary that methods for its preparation be developed. Such methods were soon available[2,9,55] and adequate supplies of this reagent were on hand at all times.

Spotted Dick Test. The so-called Spotted Dick test which was widely used by British Empire units was based upon the reaction of an N-chloramide with mustard gas to give hydrochloric acid, which in turn was detected by means of a suitable indicator. The application of this test will be described in a subsequent section.

Iodoplatinate Test. Although the iodoplatinate test is described in the open literature, the nature of the reaction is not completely disclosed. By isolation of the products formed it has been shown [92] that the reaction of sodium iodoplatinate with mustard gas and analogous sulfides consists in complex formation with platinum iodide according to the reaction:

$$[(ClCH_2CH_2)_2S] + Na_2PtI_4 \longrightarrow [(ClCH_2CH_2)S]\ PtI_4 \longrightarrow [(ClCH_2CH_2)_2S]\ PtI_2 + I_2$$

Thiourea Test. Mustard gas will condense with thiourea to give the hydrochloride, $(HN)C(NH_2)SCH_2CH_2SCH_2CH_2S(NH_2)C(NH)\cdot 2HCl$. The following have been found to be the most sensitive conditions for the test.[109] The sample in β-ethoxyethyl alcohol is treated with a solution of thiourea in the same solvent and boiled for 1 minute. The reaction mixture is cooled and diluted with 2 volumes of water, 1 drop of 2 *N* sodium hydroxide solution is added, and the mixture is warmed to 50 C (approximately) for 15 seconds, but not boiled. The mixture is cooled and an excess of nickel sulfate and 0.5 ml trichloroethane are added and the mixture shaken. A red color in the trichloroethane indicates the presence of mustard gas.

Miscellaneous Tests. For purposes of record, attention is called to a number of studies which had as their purpose the disclosure of new methods for the detection of mustard gas by either chemical [1,7,17,30] or biological means.[6,7,10,11]

31.2.2 Detection of Certain Arsenicals

Methods for the detection of arsenicals had not been extensively investigated prior to World War II. The principal method relied upon was the detection of arsenic by means of some modified Gutzeit method. For Lewisite, however, the Ilosvay test depending upon the red color produced with acetylene was principally quoted. Since these methods and the others in the open literature were inadequate, a search was made for more suitable arsenical detectors, bearing in mind that the compounds of most interest were those of the type $RAsX_2$.

Zinc Sulfate Molybdic Acid Test. Silica gel impregnated with a mixture of zinc sulfate and molybdic acid provides a direct, specific, and fairly sensitive detector for arsenicals, such as Lewisite, ethyl dichlorarsine, and methyldichlorarsine.[16] The test is very simply performed by drawing air to be tested through a tube containing the impregnated gel, waiting 1 minute, and examining the tube for the appearance of the color. A blue or green coloration at the intake end of the gel indicates the presence of an arsenical.

Cuprous Iodide Test. A test for Lewisite based upon the cuprous acetylide test was devised using silica gel impregnated with cuprous iodide. A red ring forms at the intake end of the gel layer within 30 seconds after the addition of 10 per cent sodium hydroxide solution with 3–6 μg or more of lewisite vapor.[35p]

Thiocarbazone Reagents. The use of diphenylthiocarbazone as a reagent for the detection of tripositive arsenicals [30b] suggested that other thiocarbazones might be found which would be superior to the prototype. Therefore a number of substituted diphenylthiocarbazones were prepared and their value as detectors for tripositive arsenicals determined.[19,24,27,31,32] The thiocarbazones were prepared either from the corresponding amines through the nitroformazyl or from the hydrazines through the arylthiocarbazic acid pyridine salt. Two of the substituted phenylthiocarbazones prepared, di-*p*-biphenylthiocarbazone (DBT) and di-*o*-phenoxyphenylthiocarbazone (DPT) appeared to offer promise as detectors for tripositive arsenicals.

Dianisylpropylene Reagent. Unsymmetrical diarylethylenes which contain positive, that is, electron-donating groups in the aromatic nuclei have been known for a long time to give colored addition products with a variety of substances. Twelve diarylethylenes were synthesized and tested as detectors for tripositive arsenicals. Dianisylpropylene (DAP) was found to be the most promising compound.[24] Silica gel mixed with 5 per cent dry DAP gave a color directly when exposed to 1 μg or less of ethyldichlorarsine or lewisite, but the gel mixture was not stable for many days at 60 C. In air of high humidity, the sensitivity of the test is greatly decreased.

Miscellaneous Organic Reagents. A large number of organic compounds were investigated in regard to their possible use as detectors for tripositive arsenicals.[17,23,30a] The most promising of the group investigated were several nitro compounds notably *p,p'*-dinitrostilbene-*o,o'*-disodium sulfonate and 5 (or 8-) nitroisoquinoline. The detection reaction involved

reduction of the nitro group by the arsenical in the presence of alkali to give a dyestuff.

Miscellaneous Tests. For purposes of record, attention is called to a number of studies which had as their purpose the disclosure of new methods for the detection of arsenicals by either chemical or biological methods.[1,2,6,7,16]

31.2.3 Detection of Nitrogen Mustards

The nitrogen mustards may be recognized by taking advantage of their basic properties to produce a color change in an acid-base indicator, to control the pH in a metal ion-indicator coupling reaction such as nickel-dimethylglyoxime, and to form a precipitate with reagents such as picric acid, mercuric chloride, sodium iodoplatinate, chloroplatinic acid, chlorauric acid, phosphomolybdic acid, Dragendorff's reagent ($KBiI_4$), and Mayer's reagent ($KHgI_2$).[14,22,49,114] The more important of the above tests as well as several others are discussed in the following paragraphs.

DB-3 Test. Because of their similarity to mustard gas in being alkylating agents the nitrogen mustards give a positive test with the DB-3 reagent.[22,34a,b]

Dragendorff Reagent. Among the so-called alkaloid reagents, the Dragendorff reaction proved to be useful for the detection of the nitrogen mustards.[22,34, 57,58,66] Attention is called to an improved preparation of this reagent.[66]

Miscellaneous Tests. Attention is called to several studies which had as their goal the development of tests suitable for the detection of the nitrogen mustards.[2,11,17]

31.2.4 Detection of Fluorine-Containing Chemical Warfare Agents

Detection of Fluoride Ion. In view of the absence of a reasonably specific test for many of the compounds containing fluorine, much effort was expended in trying to develop a simple method for converting covalent bound fluorine to fluoride ion and detecting the latter substance. In general either hydrolytic, oxidative, or pyrolytic methods were used for the formation of fluoride ion. British investigators favored oxidative methods of degradation allowing the detection of fluoride ion by a glass etching test.[101,104] Alternative methods of detecting fluoride ion were also studied[101,102,104b] using chromotropic acid and boric acid. Pyrolytic methods of decomposition were studied by both British and American investigators using zirconium or thorium lakes of alizarin or purpurin to detect the fluoride ion formed.[22,49,104a] An ingenious method was developed for carrying out the pyrolytic reaction[49] using the heat arising from the exothermic oxidation of methanol over platinized silica gel.

Detection of Fluoroacetate. Fluoroacetate can be hydrolyzed by alkali to form fluoride and glycollic acid. This latter substance can be converted by the action of strong sulfuric acid into formaldehyde and the latter detected with the aid of chromotropic acid.[104b]

Detection of Dialkyl Fluorophosphates. The dialkyl fluorophosphates are alkylating agents and therefore can be detected with the aid of the DB-3 reagent.[22,34] A biological test dependent upon the production of miosis by the dialkyl fluorophosphates has also been described.[68]

Detection of Disulfur Decafluoride. Approximately 30 easily oxidizable aromatic compounds including some of the better oxidation-reduction indicators were investigated in regard to their usefulness for the detection of disulfur decafluoride.[14] Of the substances investigated, *p*-phenylenediamine was found to be the most satisfactory.

31.2.5 Detection of Cyanogen Chloride, Hydrocyanic Acid and Related Compounds

Pyrazolone-Pyridine Reagent. An important reaction for the detection of cyanides and other cyanogen compounds is based upon the reaction of cyanogen chloride with a mixture of pyridine (or a pyridine derivative) and phenylmethylpyrazolone to form a dyestuff.[47] This reaction can be used not only for the detection of cyanogen chloride but also for hydrogen cyanide, certain nitriles, thiocyanates, chlorine, and chloramides.[47] For the detection of hydrogen cyanide, nitriles, and thiocyanates, preliminary treatment with chlorine or a chloramide to form cyanogen chloride is necessary. A variation of the above test is based upon the formation of a red dyestuff by the action of cyanogen chloride on a mixture of benzylpyridine and barbituric acid.[71]

DB-3 Reagent. Cyanogen chloride will react directly with DB-3 to give a red dyestuff.[34a,b,c,35] The reaction presumably involves cleavage of the carbon nitrogen bond in the pyridine nucleus and therefore differs from the reaction of DB-3 with acyl halides.[33]

Detection of Hydrogen Cyanide. The liberation of hydrogen ion by the reaction of hydrogen cyanide with mercuric chloride is well known. A mixture of metanil-yellow and mercuric chloride has proved to

be a useful reagent. A picric acid reagent has also been used for the detection of hydrogen cyanide.[59]

Detection of Ethyl Dimethylamidocyanophosphate. This compound readily hydrolyzes to form hydrogen cyanide and can be detected by any reagent suitable for the detection of hydrogen cyanide.[109]

31.2.6 General Screening Reagents

Reagents such as chloraurie acid [121,122] which will react with a large number of chemical warfare agents possess considerable utility despite their lack of specificity. These reagents can be used to determine the presence or absence of a large group of chemical warfare agents and in this manner expedite identification. Despite considerable study [28,29,34c] no reagents superior to chloraurie acid for the above purposes were discovered.

31.3 VAPOR DETECTORS FOR CERTAIN CHEMICAL WARFARE AGENTS

In the previous section tests suitable for the detection of certain chemical warfare agents were discussed without regard to application. The utilization of these and other tests in the development of practical devices suitable for the detection of certain chemical warfare agents when present in the atmosphere under field conditions will now be considered. It is obvious that detectors must be simple in their operation, rugged, and reasonably reliable. They must also be able to withstand shipment and storage under adverse conditions. The two types of vapor detectors developed and used during this war were the impregnated silica gel type and the impregnated paper type. In the former the detection reaction was allowed to take place on silica gel granules, and in the latter, on the fibers of a suitable paper.

31.3.1 Impregnated Silica Gel Vapor Detectors

The use of impregnated silica gel for the detection of chemical warfare agents was initiated at Edgewood Arsenal. In general the detectors were made by placing a 60-mm column of suitably impregnated silica gel in a 80-mm length of 2-mm glass tubing and holding the gel in position with cloth plugs. In view of the fact that an adequate summary of the various individual detectors developed during the past four years [12,35c,f,g,h,35e,f,h,i,j,51,55,65,97] is available,[34] the present discussion will be limited to the more general features of silica gel type vapor detectors.

Silica Gel. Only certain types of silica gel are generally useful for the construction of silica gel-type vapor detectors. The most satisfactory is the so-called Davidson low-density silica gel. It was found necessary to process the commercially available gel in order to reduce the iron content and to control the acidity of the gel.[35b,37a,b]

Adsorption of Sample. The silica gel vapor detector is ordinarily operated by aspirating air through the detector tube with a manually operated pump or bulb. With certain substances, suitable impregnated gels can be found which react directly with the substance or substances to be detected to give a characteristic stain or color. In other cases it may be necessary to adsorb the sample on an impregnated or unimpregnated gel and then add a liquid or gaseous reagent to complete the test. Conversely, a reagent may be added first and the sample then absorbed. In still other cases, notably with the DB-3 reagent, the sample is first adsorbed on an impregnated gel, the tube heated to facilitate the first stage of the reaction and then a liquid reagent added to complete the test.

It is generally true that all nonpersistent chemical warfare agents are poorly absorbed on silica gel and in these cases, in order to obtain reasonable sensitivity, an impregnated gel that will give a direct test with the substance to be detected must be employed. Because of this poor adsorption of nonpersistent agents by silica gel it should be remembered that even when the gel is impregnated with a reagent that will react with the substance being detected, only a fraction of the substance will be adsorbed on the gel and the stain or color will be distributed uniformly throughout the visible surface of the gel. Therefore, except under very closely controlled conditions, it is unlikely that detector tubes of the impregnated silica gel type can be used for the quantitative or even semi-quantitative estimation of vapor concentrations of nonpersistent agents, although they may be useful for their identification.

The persistent chemical warfare agents are readily adsorbed on unimpregnated silica gel, provided the absolute humidity is low. With increasing absolute humidity the adsorption process becomes less efficient, and at high absolute humidities significant quantities of agent may not be adsorbed. With impregnated silica gels the effect of water vapor may not be significant, provided the substance reacts rapidly with the reagent in and on the gel. If the reaction between substance and reagent is slow, the effect is approximately the same as in the case of the

unimpregnated gel. The behavior of the nitrogen mustards and mustard itself in the BD-3 detector tube provides an instructive example of the effect of water vapor on the performance of an impregnated silica gel-type detector tube. It is well known that the nitrogen mustards react with DB-3 much more rapidly than does mustard gas. Consequently, when air containing one of the nitrogen mustards is passed through a tube containing silica gel impregnated with DB-3, the absorbed nitrogen mustard reacts with the reagent at a fairly rapid rate and, even in the presence of large amounts of water vapor, the colored zone formed after heating and development with alkali is clearly defined and its length bears some relation to the amount of nitrogen mustard introduced into the tube. However, with mustard gas the rate of reaction with the reagent is slow, and in the presence of appreciable amounts of water vapor the agent is distributed throughout the gel column with a concentration gradient being established between the two ends of the column. Therefore, after heating and development, a diffuse stain with no sharp boundaries is obtained. The collection of tripositive arsenicals on silica gel is complicated by the fact that in the presence of water vapor these substances undergo rapid hydrolysis with the result that practically no substance gets beyond the first fraction of a millimeter of the gel column, thereby rendering detection difficult.

Sensitivity of Detectors. Extensive studies [23,26,45] [1,6,48,79] on the sensitivity of the various impregnated silica gel-type detectors demonstrated, in general, that while the sensitivity of these detectors was superior to other types of detectors, the sensitivity was profoundly influenced by temperature and humidity.

Summary. In general it may be concluded that impregnated silica gel-type detectors are useful for identifying certain chemical warfare agents or groups of chemical warfare agents but that their application to quantitative or semiquantitative problems is not warranted.

31.3.2 Impregnated Paper Detectors

Papers impregnated with appropriate reagents were studied extensively with regard to their application as practical detectors for chemical warfare agents. There is little doubt that impregnated paper detectors can be usefully employed in the identification of many chemical warfare agents although in general they are less sensitive than equivalent impregnated silica gel-type detectors. It should be pointed out that it is generally necessary to aspirate air through an impregnated paper in order to obtain a satisfactory test, although with a paper impregnated with a reagent and micronized silica gel it has been claimed that aspiration is not necessary.

Mustard Gas Detectors. Although considerable effort was expended in the development of satisfactory detector papers for mustard gas,[5,26,79,87,90,95,121] the only papers that could be considered at all practical were those based either upon the reaction of mustard gas with DB-3 or its derivatives,[35,53] or upon the reaction of mustard with an N-chloramide and subsequent detection of the hydrogen chloride formed.[86,107,124,132]

Arsenical Detectors. Despite extensive search only two general types of impregnated papers were found to offer promise for the detection of arsenicals. These were papers impregnated with diphenylthiocarbazone or its derivatives [4,21,32,35b,73b,94] and papers impregnated with potassium iodide and starch.[122,123,125] Attention is called for purposes of record to a paper for the detection of arsine [3] and investigations on the reduction of chromates by arsenicals.[5]

Nitrogen Mustard Detectors. The development of papers suitable for the detection of the nitrogen mustards received considerable attention both in England and in Canada [98,99,115–119,126,128] and a summary of this work has been prepared.[112] For field detection, an acid iodoplatinate paper was adopted.[111] A paper employing DB-3 and one using acidified phloxine has also been described.[35a,77]

Miscellaneous Detector Papers. A number of particularly useful detector papers were developed for use with a paper tape recorder. These detector papers are described in Chapter 38. Papers were also developed for the detection of vesicants in materials after decontamination[78] and for the detection of phosgene,[70] fluoride,[32] disulfur decafluoride [11,119,120] and ethyl dimethylamidocyanophosphate.[100]

31.4 DETECTOR PAINTS, POWDERS, AND CRAYONS

Detector paints, powders, and crayons were developed for the detection of liquid chemical warfare agents. They are not useful as vapor detectors. The principal use of detector paints, powders, and crayons is to define the extent and degree of hazard produced by the persistent chemical warfare agents when present as liquids.

Detector Paints

Paints suitable for the detection of liquid chemical warfare agents are of two basic types. In one type a dyestuff which is readily soluble in the chemical warfare agent to be detected is incorporated into a paint whose principal pigment is insoluble in the agent. When a droplet of liquid agent is placed on a surface covered with such a paint, the agent dissolves the dyestuff present in the area of contact thereby causing a local change of color. The other type of detector paint is based upon the chemical alteration of the pigment by reaction with the agent. This latter type of paint may respond to vapor but the sensitivity of the reaction is usually so low that such application is not recommended.

Detector Paints Depending Upon Solvent Processes. A satisfactory paint for the detection of liquid mustard gas was developed by the British. This paint contained a chrome pigment and *p*-nitrophenylazo-*β*-napthylamine (B-1) as a dyestuff. Investigations in this country were directed toward modifying the British detector paint to meet local manufacturing conditions[4,50,62,75,80] and toward the disclosure of other dyestuffs more suitable than B-1. Attention was also paid to the formulation of paints that would distinguish between liquid mustard gas and lewisite.[12,36b]

Detector Paints Depending Upon Chemical Processes. The use of a paint containing mercuric oxide has been suggested for the detection of liquid mustard gas[20] and a standard green chromate paint for the detection of Lewisite.[10]

Detector Powders

As with detector paints, detector powders may be formulated on the basis of either solvent or chemical processes. In contrast to detector paints which may be used to define the extent and degree of liquid contamination on objects selected prior to the time of contamination, detector powders are of more general application. Detector powders may be used to define areas of contamination either before or after the act of contamination and are superior to detector paints for this reason. Both in England and on the Continent considerable attention was paid to the development of detector powders and means of disseminating them. It is to be regretted that comparable interest did not prevail in this country. Although several useful detector powders were developed[4,10,36a,c,63,89,97] they were not exploited even to the extent of determining their usefulness under field conditions.

Detector Crayons

Detector powders may be used in the form of a detector crayon or chalk. Detector crayons as such are useful for detecting the presence of liquid or high vapor concentrations of certain chemical warfare agents, for example, in the case of leaking munitions. The crayon may also be reduced to a powder and used in this form. Attention is called to detector crayons that have been developed for the detection of mustard gas, arsenicals, and the nitrogen mustards.[10,51,56,63,64,72,75]

34.5 DETECTOR KITS

A number of kits were developed in order to provide means for the detection of certain chemical warfare agents particularly under field conditions. As these kits were designed for use in forward areas, reliability was necessarily sacrificed for mobility and ease of operation. *In general these kits are capable of providing presumptive evidence in regard to the possible presence or absence of a restricted group of chemical warfare agents. There is no doubt that some of them are very useful for purposes of restricted identification. There is also no doubt that none of these vapor detector kits is capable of giving reliable quantitative information or even semiquantitative information in regard to the concentration of a particular chemical warfare agent although they have been advocated for this use.*

British Vapor Detector Kit.[36,91,98,108,110] This kit provides for the detection of mustard gas and the nitrogen mustards. A Spotted Dick test paper is used for the detection of mustard gas and an acid iodoplatinate paper for the detection of the nitrogen mustards. Considerable difficulty has been encountered in using this kit under tropical conditions.[112,120] Although this kit could be improved in detail, it has many commendable features. Its use for quantitative or semiquantitative purposes[98] is extremely questionable.

M-9 Vapor Detector Kit.[36,50] This kit which has been standardized by the Chemical Warfare Service contains impregnated silica gel-type detectors. It provides for the detection of mustard gas, the nitrogen mustards, arsenicals, cyanogen chloride, and phosgene. It could be readily modified to provide for the detection of hydrogen cyanide. There is little doubt that for intelligence purposes the M-9 kit is superior to all foreign kits with regard to both sensitivity and versatility. However, it is incapable

of providing reliable quantitative or semiquantitative information and in its present form is not particularly convenient to use.

Navy Mark I Vapor Detector Kit.[39] In this kit impregnated silica gel detector tubes are provided for the detection of mustard gas, the nitrogen mustards, phosgene, Lewisite, cyanogen chloride, and hydrogen cyanide. A crayon for the detection of mustard gas is also included. In general this kit resembles the M-9 detector kit although it has greater versatility and is superior to the M-9 kit in regard to ease of operation.

Security Division Detector Kit.[70] A kit intended for use by the Security Division at Edgewood Arsenal provided for the detection of mustard gas, the nitrogen mustards, Lewisite, hydrogen cyanide, cyanogen chloride, and phosgene, using silica gel detectors, impregnated papers, and reagent solutions. The kit appears to be satisfactory for the purpose for which it was designed.

Detector Paper Kit.[82] A kit containing three impregnated papers and one reagent, contained in sealed capillaries, was developed as an adjunct to the M-9 kit. Provision was made for the detection of mustard gas, the nitrogen mustards, the arsenicals, phosgene, hydrogen cyanide, and cyanogen chloride. No provision was made for aspirating air through the impregnated papers. Both sensitivity and specificity were low.

OCD Detector Kit.[36m] A kit was developed for possible use by the Office of Civilian Defense. It consisted of two separate units. The first, a portable detector kit, could be carried to the scene of an incident and the second, a set of reagent solutions, could be used to identify or confirm the identification of any agent detected by the portable detector kit. The portable detector kit contained a screening tube which had two gel sections. The first gel section contained metanil yellow, DB-3, *p*-dimethylaminobenzaldehyde and *sym*-trimethoxybenzene. The second part of the gel contained metanil yellow, sodium acetate, and mercuric chloride. In using the tube, a sample of suspected air was drawn through the tube and the intake section of the tube was cautiously heated until the mercuric iodide changed color. If the tube did not show any direct color, nonpersistent agents were absent. If no test was obtained after development, persistent agents were absent. The second section contained: (1) 50 screening tubes, contained in two screw-capped vials, (2) 50 sampling tubes, contained in two screw-capped vials, (3) one small bottle filled with 10 per cent NaOH solution and provided with a medicine dropper, (4) one tube or bottle containing aniline adsorbed on pumice, and (5) one rubber bulb, pump, bellows, or other source of vacuum.

Detector Kit For Blister Gases.[47,49,73a,b,d,e,f,g] A kit was developed for detecting the presence of vesicant chemical warfare agents on foods and food packaging materials. This kit provided for the detection of mustard gas and its homologs, cyanogen chloride, the nitrogen mustards, the arsenicals, and certain toxic heavy metals. This kit is particularly noteworthy because of its employment of ingenious silica gel paper compositions.[61]

Water Testing Kit.[31,33k,49,73c,82] A kit was developed which had for its purpose the detection of contamination of raw water by chemical warfare agents. Provision was made for the detection of mustard gas and arsenicals, and for the determination of the *p*H and chlorine demand. This kit was intended for screening purposes only and its findings were subject to confirmation through use of a more elaborate kit described in Chapter 39. Reference is made to Canadian and British kits designed for similar purposes.[127]

Enemy Detector Kits.[46] It is of interest to note that the detectors employed in enemy detector kits were universally inferior in sensitivity and specificity to those present in American or British kits. The German detector kit [42,44] was noteworthy because of its ingenious although complicated construction and the Japanese Naval Type detector [41,43,46] because of its clever aspirating device. The reference cited above contains a tabular summary giving the number of tubes and original color; the agents detected and the color produced; and also the interferences which affect the reliability of the test of each of the following kits: British Kit, Mark II, Pocket Vapor Detector, German Chemical Agent Detector Kit, Japanese Chemical Agent Detector Kit, Japanese Naval Type Chemical Agent Detector Kit, Japanese Gas Detector Kit B, Japanese Gas Detector Kit A, Italian Detector Kit for mustard and phosgene, and Chinese Agent Detector Kit.

Miscellaneous Detector Devices. For purposes of record, attention is called to several devices proposed for the detection of mustard gas, the arsenicals, and fluorine-containing toxic agents.[7,20,32]

Chapter 35

IDENTIFICATION OF CHEMICAL WARFARE AGENTS

By *Carl Niemann*

35.1 INTRODUCTION

THE RAPID AND ACCURATE identification of chemical warfare agents used by enemy forces is necessary for the development of effective countermeasures. One has to guard against the eventuality of the use not only of a recognized agent but of new ones as well. By providing means of identification at a number of organizational levels, characterization can be expedited although it is clear that only limited information can be expected from forward groups. In practice it would appear that forward groups should not be asked to provide information beyond the possible presence or absence of recognized agents or the possible presence of a new agent. Their primary function should be the procurement of suitable samples for rear area establishments. Thus proper provision for chemical intelligence should include semipermanent laboratory units capable of performing all tasks necessary for the complete identification of recognized and new chemical warfare material as well as portable kits of more limited applicability for use in forward areas.

35.2 LABORATORY IDENTIFICATION OF CHEMICAL WARFARE AGENTS

In order to insure the rapid, positive identification of both recognized and new chemical warfare agents and material, adequate laboratory facilities must be provided. These can be obtained only in a semipermanent installation. Mobile laboratories, although fascinating in some respects, are too limited in applicability to be charged with primary responsibility for positive identification of new chemical warfare agents or material. This section will be confined to the facilities and procedures required in semipermanent installations.

35.2.1 Laboratory Facilities

A military laboratory differs from a civilian one in that the former must be capable of operation in regions devoid of the usual facilities associated with developed urban areas. In order to provide for the establishment of a self-sufficient laboratory it was assumed [28a] that (1) the laboratory in question would be a semipermanent installation, (2) it would be staffed by individuals skilled in the practice of chemistry, (3) the staff would consist of three to six chemists continuously employed, (4) the duties of the laboratory would be principally of an analytical nature, (5) the analytical tasks to be anticipated would be those arising from chemical warfare problems, and (6) the laboratory must be capable of operation for a period of 6 months in regions remote from sources of supply. Starting with the above information and assumptions, the needs of a Theater of Operation chemical laboratory were considered and detailed recommendations were made.[28a] In general the recommendations in regard to equipment, apparatus, and supplies were made on the basis of assumed adoption of milligram or centigram procedures; these techniques allowed ease and rapidity of manipulation, afforded a concomitant economy of reagents and chemicals, permitted the use of apparatus that was much less bulky than that encountered in decigram, gram, or multigram procedures, and introduced a considerable factor of safety when working with noxious, toxic, or explosive substances.

The above cited recommendations provided the basis for the procurement of the so-called Chemical Laboratory Companies and, on the basis of actual operation of these units in overseas areas, it appears that in general adequate laboratory facilities were provided.[43]

35.2.2 Laboratory Procedures

Given sufficient time and adequate facilities there is little doubt that competent chemists can identify practically any substance. However, in view of the need for rapid identification, it was considered advisable to provide laboratory personnel with various schemes in order that identification might be expedited.

Procurement of Sample. The first requirement of any scheme of analysis is procurement of the sample. Although in most instances samples of chemical warfare agents may be obtained from unexploded and malfunctioned munitions, it was thought necessary

to consider the collection of samples from other contaminated materials, such as soil, foliage, and masonry. The results of this study [29b] and others [30,44] proved to be of value in considering the design of a field sampling kit.[40,58] Soil, foliage, or air sampling is of limited applicability and a really satisfactory general solution of this problem has not been attained.

Separation and Purification of Sample. The next step in the systematic scheme of identification was consideration of a system suitable for the separation and purification of chemical warfare agents. While conventional methods familiar to any competent organic chemist suggested themselves, the advantages of micro and semimicro procedures soon became evident. A system of procedures for the separation and purification, by distillation or sublimation, of 50- to 300-mg quantities of chemical warfare agents was therefore developed.[23] The distillations were performed with an efficient microfractionating still at 2- to 760-mm pressure, a molecular still at 0.001- to 1-mm pressure, or a sublimation apparatus at 0.001 to 760 mm. The procedures were not generally applicable to the separation of components boiling below room temperature although provision was made for their collection. Even though distillation is the most general and easily systematized method for purifying unknown samples, it should be emphasized that distillation or sublimation will not be suitable for substances that decompose on heating before they attain a vapor pressure of at least 10^{-3} mm (the lowest pressure obtainable without the use of a diffusion pump). In those cases where distillation is found to be impossible, other purification methods such as crystallization, or methods involving partition between solvents have to be employed. Procedures were also included for the determination of certain physical constants in order to determine appropriate purification methods, and to check the separation effected by these methods.

Ultimate Analysis. The advantages of early knowledge of the elementary composition in the characterization of both organic and inorganic compounds led to the providing of procedures not only for the qualitative identification of certain acidic elements likely to be found in chemical warfare agents [22] but also a system for the ultimate analysis of chemical warfare material by which one could obtain not only qualitative but also quantitative information regarding the elementary composition.[4,21,28] This latter system of ultimate analysis was used extensively by laboratory company personnel for the analysis of a great variety of substances including canister carbons and ordnance materials.[48]

For the qualitative identification of certain acidic elements [22] the zinc dust-calcium oxide fusion method was adapted to the detection of nitrogen, the halogens, arsenic, sulfur, and phosphorus, using single 1-mg samples; and for carbon and fluorine using separate 1-mg samples. The methods were applicable to compounds having a boiling point higher than approximately 60 C, and any one of the above elements could be detected in the presence of any of the other elements when present to the extent of 1-5 per cent of the sample weight.

The system for the ultimate analysis of chemical warfare agents [4,21,28] consists of three parts. Part I [4] provides procedures for decomposing the sample by a fusion with sodium peroxide in a suitable bomb. The sample can be a solid or it can be a liquid with a boiling point higher than 40 C. The sample can also be a liquid or gas with a boiling point below 40 C provided that it is sealed in an appropriate glass capsule.

Part II [4] of the systematic scheme provides procedures for the systematic detection and semiquantitative determination, by volumetric or colorimetric methods, of arsenic, boron, bromide, chlorine, chromium, fluorine, iodine, phosphorus, selenium, silicon, sulfur, and tellurium. Procedures are also described for the quantitative determination of nitrogen, carbon, and hydrogen. The procedures employ techniques commonly used in semimicroanalysis. Sample weight requirements are, 10-20 mg for detection and estimation of those elements provided for by the systematic analysis, and 15-30 mg for the determination of carbon or carbon and hydrogen. The sensitivity of the detection of those elements provided for in the systematic analysis is 1 per cent of the sample, that is, any of the elements mentioned above which constitute as much as 1 per cent of the original sample should be detected. The accuracy of the estimation of those elements provided for in the systematic analysis is ± 0.3 mg in a 10- to 20-mg sample; that is, the amount of element present can be estimated to within a deviation of ± 0.3 mg. However, deviations as much as ± 0.8 mg may occur with certain elements present in large quantities. The accuracy of the determination of nitrogen is ± 0.1 mg, that of carbon by the dry combustion method is ± 0.05 mg, and by the wet combustion, ± 0.05 mg.

Part III of the systematic scheme [28] provides for

the systematic detection and semiquantitative estimation of those basic elements which may be encountered in the analysis of chemical warfare agents. Those elements are included which are likely to be encountered as constituents of toxic agents and their containers, incendiaries, pyrotechnic agents, and protective equipment. These elements are (in the order of their detection and estimation) iron, titanium, manganese, nickel, cadmium, magnesium, barium, strontium-calcium-selenium, tellurium, copper, lead, zinc, arsenic, antimony, tin, and chromium. Methods for aluminum, silver, and potassium were also included. These methods are applicable to most organic and inorganic compounds which are not resistant to fusion with sodium peroxide. A 10- to 20-mg sample is needed for the analysis. A basic element can be detected if it comprises at least 1 per cent of the sample. The analysis is made on the residue and the solution resulting from a sodium peroxide fusion identical with that employed in the analysis of acidic elements and, when desired, a larger sample can be used for a single fusion for both systems.

Directions for preparing the reagents used in the above system, a list of apparatus required, the amount of reagents needed, a description of the required techniques, and specifications for the construction of special apparatus have been provided.[21,27,28] In addition, an outline was prepared [28] for a course of instruction consisting of lectures and laboratory work, which has as its purpose the training of personnel of the analytical section of the Chemical Warfare Service [CWS] M-2 Chemical Laboratory Company. The course required 6 weeks, 8 hours per day, 6 days per week.

Functional Group Analysis. A system for the identification of functional groups present in chemical warfare agents has been devised,[24] which had for its purpose the identification of either the simple or complex functional groups which may be present in organic chemical warfare agents containing any of the following elements: oxygen, chlorine, bromine, iodine, fluorine, nitrogen, sulfur, arsenic, and phosphorus. Consideration has been limited (1) to functional groups present in a large number of compounds which were tested and found to have toxic or vesicant properties either by investigators working at Porton or the University of Chicago Toxicity Laboratory, (2) to functional groups present in compounds which are known to be effective irritants,[25] and (3) to functional groups which occur in the hydrolysis or oxidation products of some of these compounds or which occur in the common impurities of some chemical warfare agents. The system was not intended to provide for the identification of a particular compound but was part of a general scheme devised for that purpose. The application of the system requires (1) that the test substance be known to contain carbon, (2) that qualitative information as to the presence of elements other than carbon, hydrogen, and oxygen be available, and (3) that it be a pure compound. The system is committed to operations on a milligram scale with the result that only 15–30 mg of purified test substance are sufficient for a complete series of tests.

In general the system consists of systematic tests and includes (1) general tests, used on all unknowns, to determine whether the substance is acidic, neutral, or basic and whether it is an oxidizing or reducing agent, and (2) restricted tests, applied only in certain cases depending upon the elementary composition of the unknown. Tabular summaries are provided for the rapid correlation of observed test behavior with the behavior of individual functional groups. Detailed directions for the manipulation of milligram quantities of test materials, a list of apparatus and equipment needed for the system, and a list of reagents required and their preparation are given in a series of appendices.[24,28]

Derivatization. Application of the above schemes to the identification of an unknown chemical warfare agent usually results in limiting the unknown to a particular group of possible compounds. Positive identification can then be accomplished by derivatization and direct comparison or, if the compound has not been previously described, by transformation into known compounds. In order to facilitate identification in those cases where the compound had previously been prepared, procedures were developed for the derivatization of the more common chemical warfare agents and the melting points of the derivatives determined.[22–26,28]

Tabular Summaries. In order to provide adequate data with respect to the physical constants of the more common toxic chemical warfare agents, the literature was examined for 100 compounds, 11 of which were specially selected because they were considered as probable aggressive agents. The review [29] was intended to supplement Chemical Warfare Service Field Laboratory Memoranda previously issued.[31,32,33,36] The physical constants considered were (1) molecular weight, (2) elementary composition, (3) boiling point, (4) vapor pressure, (5) melting

point, (6) density, and (7) refractive index. These properties were organized in the form of indices, the compounds in general being arranged according to increasing values of the property.

Microscopic Methods. In order to augment, and in some instances to extend, the potentialities of the above methods of identification, investigations were undertaken to provide microscopic methods for the identification of (1) derivatives of chemical warfare agents,[7,9-11,13,15-17,19] (2) solid chemical warfare agents,[2,5,8,12] and (3) certain elements present in chemical warfare agents.[17,18] This program was subsequently expanded to include the microscopic characterization of selected explosives.[3] The derivatives covered in this study comprised the more important ones for the common agents. In the course of the work some 136 compounds presenting 199 different crystalline phases have been described optically and geometrically, all but a few of them for the first time. A compromise was made between ideal completeness of descriptive data and what information was most readily obtainable on samples as they might be studied in the Chemical Laboratory Companies. Emphasis was placed on properties that are distinctive and easy to observe, and on methods that will insure their ready and consistent availability. The descriptions are in accordance with standard practice, and should be usable by anyone having a foundation in microscopic crystallography.

In most instances a few of the more obvious characteristics will suffice for recognition of an agent or derivative, so that the observer should be able to identify unknowns without resorting to all the details of the descriptions reported. The inexperienced microscopist will be greatly aided in this by comparisons with the sets of samples that are part of the equipment of the Chemical Laboratory Companies. Several special techniques not previously emphasized were developed and found particularly useful in this work.

It was possible in a number of instances to develop rapid methods for the identification of agents by making use of crystalline derivatives that are readily prepared on a micro scale and also by applying the well known reactions of microscopic qualitative analysis for the identification of certain elements. The work carried out along this line included microscopic studies of all solid agents thought to be of interest, and, since many of these exhibit characteristic crystalline properties, direct identification without derivation is possible. Descriptions and methods for the microscopic identification of the common high explosives and primer ingredients were prepared for the use of the Chemical Laboratory Companies.

Microscopic procedures are particularly appropriate because the derivatives obtained are identified by melting point and crystallographic study to afford a number of additional characteristic criteria with which to confirm an identification. Derivatization reactions can ordinarily be applied to previously fractionated and purified samples, but microscopic identification usually does not require such a high degree of purification of the derivatives or separation from mixtures, diluents, thickeners, etc. Many of the derivatization reactions can be carried out under the microscope often with impure samples or mixtures of agents to yield directly derivatives of characteristic crystallographic properties.

Summary. In view of the fact that the laboratory companies were provided with adequate library and laboratory facilities in addition to being supplied with the above and other identification procedures,[27] considerable confidence could be placed in their ability to identify rapidly both recognized and new chemical warfare material. Events proved that this confidence was justified.[43] It should be pointed out that a number of other schemes for the identification of chemical warfare agents have been proposed [25,26,31,34,38,61] but almost without exception they were considered inadequate for the purposes of a semipermanent laboratory unit although admittedly useful in other circumstances.

35.3 IDENTIFICATION OF CHEMICAL WARFARE AGENTS IN MOBILE LABORATORIES

Mobile laboratories intended for purposes of chemical intelligence were developed and used by both Canadian [34] and British [31,32] units. There is no doubt that a mobile laboratory offers considerable challenge to the ability of designers; unfortunately, the limitations of space so restrict the scope of such laboratories that they cannot be considered as a replacement for a well-equipped semipermanent installation. It would appear that mobile laboratories are of utility only in those cases where the problems they may encounter are clearly defined as, for example, identification of recognized agents, surveillance of issue material, routine testing, and meteorological studies. As mobility should not be confined to areas traversable by wheeled vehicles it does not seem wise to tie the

laboratory to any one type of transportation, be it vehicle, boat, or plane. There are too many situations where any one type of transportation may be inadequate. Therefore, if a mobile laboratory is desired, it would appear that the best solution is to develop the laboratory around a series of portable kits, each designed for a specific task. Thus for any one type of mission certain kits could be selected, depending upon the task at hand. A mobile laboratory assembled upon the above principles would consist of a series of kits, each series designed for a specific task (for example, the identification of recognized chemical warfare agents), and each series of kits composed of component kits of varying portability and scope. Thus, depending upon the situation, a kit could be selected that would be of maximum utility consistent with the site and circumstances of its intended operation, bearing in mind that extent and reliability of operation will decrease with the size of the kit.

The so-called M-3 mobile laboratory[39] of the Chemical Warfare Service was probably the closest approach to the above type of laboratory unit attained during the war but it was not possible to assemble a particularly satisfactory unit, principally because of the lack of time. However, some of the kits contained in the M-3 laboratory are very useful and it is suggested that a satisfactory mobile unit could be assembled if advantage were taken of the kits developed, not only in this country but also abroad. In the following section a number of kits designed for the identification of recognized chemical warfare agents are described. Consideration is also given to methods of identification capable of being developed into self-contained kits even though the actual kit may not have been constructed or described.

35.3.1 Kits Developed for Identification of Recognized Chemical Warfare Agents

British War Gas Testing Case. The War Gas Testing Case[46-49] was designed to provide a compact and portable set of apparatus and reagents for the identification of the recognized chemical warfare agents. With its aid it is possible to determine, with a considerable degree of certainty, the identity of many of the common war gases, and in those cases where exact identification is not possible, much valuable information can be obtained. The instructions provided are intended as a guide to the use of the case and its potentialities; they are not intended to describe a rigorous routine of testing and do not fully exhaust the possibilities; individual judgment and particular circumstances are relied upon to determine the exact procedure and deductions made. In general the equipment contained in the cases provides for identification by means of reactions in solutions, such as formation of a precipitate, color, etc., or by reactions with papers containing appropriate reagents. The kit contains many attractive features and is of surprising applicability considering its size.

CWS Chemical Agent Analyzer, E-10. The collection of chemical warfare agents on plain or impregnated silica gel and subsequent identification of the collected agents by means of color reactions with or without the addition of supplementary reagents was studied extensively in this country by both the Chemical Warfare Service and the National Defense Research Committee. One of the first schemes developed was designed to provide for the identification of 32 selected compounds, which included all of the more important recognized chemical warfare agents except smokes, after collection of the sample on plain silica gel tubes.[1,14] This scheme was subsequently adapted for use in a kit designed by CWS and designated as Chemical Agent Analyzer, E-10.[4] This kit contained sufficient equipment and reagents to provide for the identification of mustard gas, the nitrogen mustards, arsenicals, phosgene, cyanogen chloride, hydrogen cyanide, chloropicrin, phenacyl chloride, and bromobenzyl cyanide by means of impregnated silica gel tubes or papers, and for the identification of some 20 less common, recognized agents through the use of either plain or impregnated silica gel tubes and supplementary reagents. The scheme provided for the identification of about 32 toxics, both persistent and nonpersistent, and the procedures were organized in the form of a series of definite directions to facilitate identification of the agent. The effects of mixtures on the scheme were studied, as were the effects of some screening smokes and of high humidity; all were found to present serious interference under certain conditions. Each test was studied rather critically, and the sensitivity, length of time after exposure which will still allow detection, and possible interfering substances were determined. Because of the possible value of a quick, simplified scheme, a system was devised which needs only three exposed tubes. This simplified scheme included most of the important toxics and allowed their assignment to one of several classes, but it did not allow for complete identification.

A number of new tests were included in the scheme,

among them the DB-3-1 and the selenious acid test for the nitrogen mustards. The former depends on the fact that thionyl chloride inhibits the DB-3-160° test with nearly everything except the nitrogen mustards. The DAS test for chloropicrin is also new and consists of decomposing the sample with sulfuric acid containing barium diphenylamine sulfonate. Nitrosyl chloride, which is formed from chloropicrin, oxidizes the reagent to a blue purple. Other new tests include the test for hydrogen cyanide and cyanogen chloride, a test for nitrites and KB-16 using sulfanilamide and N-(1-napthyl)-ethylenediamine, a hydroxamic acid test for methyl fluoroacetate, tests for phosphate and fluoride ion after decomposition of fluorophosphates on the gel by hot nitric acid, and tests for lachrymators using 2,4-dinitrochlorobenzene or 4,6-dichloro-1,3-dinitrobenzene. The E-10 kit and its system of identification of recognized chemical warfare agents possesses considerable merit and is generally satisfactory for the tentative identification of agents present in the atmosphere. In view of the possibility of anomalous behavior of certain of the tests under certain situations, it is clear that information obtained through the use of the kit should be subject to confirmation by unambiguous methods. One disadvantage of the present kit is that its applicability in general is limited to those cases where vapor samples can be obtained. Some consideration should be given to the tentative identification of the relatively nonvolatile hydrolysis products of certain of the more common, recognized chemical warfare agents.

Smoke Identification Kit. A scheme and kit for the detection and identification of materials which might be encountered in smokes was developed[4,30] and 15 units were supplied to the Chemical Warfare Service. The following agents were considered in the scheme: cadmium chloride, cadmium oxide, phenacyl chloride, diphenylchlorarsine, diphenylchlorarsine oxide, diphenylcyanoarsine, phenarsazine chloride, phenarsazine oxide, phenyldichlorarsine oxide, sesquimustard, selenium dioxide, sulfur, ricin, phosphoric anhydride, zinc chloride, and zinc oxide. Three quick preliminary tests were used to determine the presence or absence of the toxic agents mentioned, with the exception of ricin. The detailed analysis is complete for many mixtures of these agents and the known cases of interference, using the separations indicated in the scheme of analysis are given in the descriptions of the tests. The preliminary tests require two samples. The complete analysis depends upon the separation of the agents by extraction and requires from five to ten tubes depending upon the size of the samples. The above kit appears to provide a satisfactory means for the identification of generally recognized toxic and nontoxic smokes.

Miscellaneous Detector Kits. The Chemical Agent Detector Kit, M-9, the Navy Mark I Vapor Detector Kit, the Security Division Detector Kit, the Detector Paper Kit, the Detector Kit For Blister Gases and the Water Testing Kit described in Chapter 31 are suitable for the tentative identification of the more common chemical warfare agents. These kits, or their components, should find application in a mobile laboratory. Attention is also called to a system of identification,[42] adopted from German practice,[30] which is based upon aspiration of air through or over a sample of contaminated earth or foliage and then through a series of bubblers containing suitable reagents.

Chapter 36

FIELD SAMPLING OF PERSISTENT CHEMICAL WARFARE AGENTS UNDER SUBTROPICAL AND TROPICAL CONDITIONS

By *Carl Niemann*

36.1 INTRODUCTION

Prior to 1943 no attempt had been made to study the behavior of persistent chemical warfare agents in tropical or subtropical areas. In contrast, considerable experience had been obtained in conducting field trials with persistent chemical warfare agents in continental areas in the temperate zone, notably at the Suffield Experimental Station in Alberta.[42] Unfortunately the topography at Suffield was that of a typical semiarid prairie and, consequently, sampling techniques used at that station, although possibly satisfactory for the purposes of the station, were so specialized as to lose all applicability to other topographical situations. The practice at the Proving Ground at Dugway, Utah, was equally specialized. Although the Porton establishment in England was a pioneer in the development of field sampling methods,[22,43] investigations at this station were on such a small scale that specialized sampling techniques again appeared suitable. *At all three of the above stations the sites were notably exposed and there was ready access at all times to all points in the sampling areas.* This highly specialized topography permitted the use of sampling methods and devices that were practically useless elsewhere. The factors that prevented the application of the sampling techniques developed at the foregoing stations to tropical and subtropical situations were topography, temperature, and humidity.

In the years 1943 to 1945, experimental stations were established in Florida, Queensland, Panama, India, and New Guinea. Although all of these stations conducted extensive field trials with mustard gas, the Bushnell, Florida, establishment was outstanding in the development of chemical sampling techniques of general applicability. The methods developed and used at this station, which relate primarily to the chemical sampling of mustard gas vapor, have been described,[13] and much of the information contained in this discussion has been drawn from experience at Bushnell supplemented by observations at some of the other stations.

36.2 DETERMINATION OF TOTAL VAPOR DOSAGES

The determination of the total vapor dosage present over a selected time interval at a given point in the sampling area is of paramount importance in the field assessment of a chemical warfare agent or munition. The salient features of this determination are discussed below.

36.2.1 Location and Distribution of Sampling Points

Area versus Line Sampling. The distribution of sampling points along successive parallel lines which are normal to the mean wind direction was advocated and practiced by British Empire establishments, as was a variation of this procedure wherein sampling points were placed along successive parallel arcs whose lengths were determined by the maximum anticipated variation in wind direction.[21,39-42,53] The distances between the parallel lines or arcs were usually rather large, in most cases being greater than 100 yards. It appears that this practice was adopted because of the desire to obtain data that could be applied to a theory of gas diffusion that related density of contamination and meteorological conditions to axial downwind dosages.[28] Later when work was undertaken under conditions of low wind velocity with concomitant 360-degree variability of wind direction, the arcs were closed to form concentric circles or the lines to form concentric squares, but the distance between any two circles or squares was still kept quite large. It is not sound practice to be tied to any one theory when collecting primary data and it was recognized at Bushnell that line sampling in all its variants was inadequate.[13] In contrast to line sampling, area sampling implies sampling at points dispersed with sufficient density over an entire area, so that the procurement of representative samples is insured. The increased expenditure of sampling equipment is more than compensated by the value of the data obtained by this technique.[10,14] It is be-

lieved that area sampling represents the best general practice.

Distribution of Sampling Points over an Area. The distribution of sampling points over an area so as to secure representative sampling is profoundly influenced by practical elements. Supply, time, and manpower usually determine the number of available sampling appliances and in any practical situation it is necessary to decide to what extent the density of sampling points can be reduced and still obtain representative and reliable sampling over as large an area as possible. With a single point source, probably the most satisfactory arrangement of sampling points is on a spider-web, radial-type grid.[12] Since the decrease of dosage is great with an increase of distance from the source, particularly under lapse conditions, the sampling points should be concentrated around the source and may then decrease in density with increasing distance from the source.[12] It is clear that a spider-web, radial-type grid can be used only for point sources statically generated. For this reason a simple regular rectangular grid with a grid interval of about 20 yards and the sampling points disposed on the grid line intersections is probably the most generally useful sampling arrangement,[13,42] provided topographical features are reasonably uniform over the entire sampling area. Where time and manpower are not available for the emplacement of large numbers of sampling units or where the supply of sampling units is limited, a modified rectangular grid may be employed without too great a sacrifice in accuracy.[13] In this latter arrangement sampling points are first disposed over the entire sampling area on the intersections of a 40-yard interval grid and then an additional set of sampling points are placed in the anticipated impact area on the intersections of a second 40-yard interval grid which is displaced 20 yards in both directions with reference to the first grid.[13] With this latter arrangement it is desirable to provide for a reserve of mobile sampling units which can be placed within 10 yards of the source once it has been located.[13] These mobile sampling units are disposed on a line drawn from the source through at least one line of fixed sampling points.

Vertical Distribution of Sampling Points. There is little doubt that in practically all of the field trials conducted during the past 4 years insufficient data were obtained in regard to the distribution of dosage relative to the vertical component,[10] i.e., height above ground level. It is true that this measurement adds enormously to sampling difficulties and it is not known to what extent such measurements should be made. It is clear however that limitation of sampling to the arbitrary 12- and 66-inch levels [13] may not be fundamentally sound and it must remain for future work to determine to what extent, at what intervals, and under what conditions of topography and meteorology, sampling at a number of different heights would yield data of such value [10] as to justify the obvious increase in sampling difficulty.

Distribution of Sampling Points with Reference to Topography. On level, uniform terrain a 20-yard interval, rectangular sampling grid or a superimposed double 40-yard interval, rectangular sampling grid is generally satisfactory.[13] However, if the terrain is variable it is particularly important to provide for a greater density of sampling points at sites of irregularity or of special interest. Thus, boundaries between forests and fields, openings in forest canopies, changes in density and height of forest canopies, areas of dense undergrowth, shore lines, significant changes in elevation, narrow defiles, steep irregular slopes, caves, occasional man-made structures, etc., all require special consideration in regard to the location of additional sampling points. This discussion has been confined to irregularities in topography such as occur in uninhabited or sparsely inhabited areas. What precautions are required for accurate sampling in metropolitan areas remains a matter for conjecture, very little reliable information is available.[24,25]

36.2.2 Duration of Sampling Periods

Continuous versus Intermittent Short-Time Sampling. This discussion is confined to practices purporting to give reliable information regarding the mean vapor concentration over a time interval of approximately 4 6 hours. A major difference in the sampling practice of British Empire and American establishments was the preference of the former for intermittent sampling and of the latter for continuous sampling. There can be no doubt that continuous sampling over the entire time interval, in this instance 4 6 hours, will give reliable information regarding the mean concentration attained during the selected time interval, provided, of course, that the performance of the sampling device is satisfactory throughout the entire sampling period. As this latter condition can be satisfied within reasonable practical limits,[1,13] the practice of continuous sampling over time intervals of 4 6 hours is sound and practical.

In intermittent sampling the practice involves

taking samples for periods of 10–30 minutes beginning the sampling periods at, for instance, zero time, 0 + 30 minutes, 0 + 1 hour, 0 + 2 hours, etc.[12] This practice is based upon the assumption that the change of concentration with time is continuous and regular and that the total dosage can be obtained by integration of the concentration versus time curve. While this practice may be satisfactory when used on open level terrain with low ground cover, with a wind velocity greater than 5 mph, and the variability of wind direction small, it is certain that under forest conditions where the wind velocity is low, the wind direction exceedingly variable, and the distribution of obstructions irregular, the practice leads to serious error.[5,12] If the terrain were rugged and variable the situation would be far worse. Aside from the above objections to intermittent sampling as a general practice there are practical elements to consider. If the sampling devices are not capable of completely automatic operation an extremely large number of people is required to perform the necessary operations. Even under ideal conditions there is an appreciable error introduced in timing the sampling periods at different sampling points, and, where personnel are required to wear protective clothing, operation becomes more unsatisfactory because of augmented fatigue.

Prolonged Sampling. In some cases significant amounts of vapor may be evolved from a contaminated area for a period of several days. The problem of determining the total vapor dosage under these conditions deserves special consideration. At first sight it would appear that taking successive 4- to 6-hour samples over the entire sampling area for the entire period would be necessary. While this practice would certainly give reliable data it is also extremely wasteful of manpower and would require an enormous reserve of sampling accessories. It is not possible to prescribe a procedure that will fit all cases; all that can be done here is to point out the more important considerations. After information has been obtained during the first sampling periods with respect to the behavior of concentration with time at certain selected points in the sampling area, it has been found possible to predict with reasonable accuracy the extent to which sampling must be carried out during succeeding sampling periods. In such predictions it is extremely important to take into account any anticipated variation in meteorological conditions. For example, if the end of the first sampling period falls in the early morning hours it is quite possible that vapor concentrations will be very low at the end of this 4- or 6-hour period and may remain so until shortly after sunrise. However at this time the vapor concentration may rise rather abruptly and if this possibility has been overlooked in deciding which sampling positions should be operated during this second sampling interval, it is clear that considerable error in overall total dosage values will result. As a similar effect may be produced by a light rain, it is clear that prior to the beginning of a sampling period there must be at hand reliable information not only with respect to predicted concentrations at the beginning of the sampling period but also a forecast for the next 4–8 hours of the meteorological factors influencing the propagation of gas clouds. This information includes presence or absence of clouds, fog and rain, ground and air temperatures, and time of sunrise and sunset. In practice it is usually found, barring complicating meteorological factors, that the extent of sampling can be profoundly decreased after the first or second sampling periods and confined for the most part to impact areas.

An important effect arising from the prolonged sampling of an impure agent such as Levinstein mustard gas was observed at the Bushnell installation.[13] In the sampling of areas contaminated with Levinstein mustard it was observed that some of the less specific analytical methods such as the bromine titration, chloramine-T colorimetric method, etc., although satisfactory in the determination of mustard gas in samples taken during the initial period, gave results greatly in error when applied to samples taken during the later sampling periods. The explanation of this phenomenon lies in the fact that during the initial sampling period the ratio of mole fraction of mustard gas to mole fraction of interfering, less volatile impurities was large enough to mask the effect of the interfering substances. During the later sampling periods, because of the greater rate of loss of the more volatile component, the ratio became small enough to produce a serious and profound error. This effect should serve to emphasize the need for evaluation of the specificity of analytical methods and instruments with respect to all possible components at various relative concentrations.

36.2.3 Nature of Sampling Device

There is little doubt that the most satisfactory way to obtain reliable information regarding the mean vapor concentration prevailing over a selected time interval at any one sampling point is to provide for

the aspiration of a known volume of air through a bubbler charged with a suitable absorbent and subsequent determination of the amount of substance contained in the absorbing liquid. As this procedure gives the integrated concentration over the selected time interval, it is clear that this method is more sensitive and more accurate than procedures which depend upon the use of an instrument which records concentrations present at any one time as a function of time, followed by graphical integration of the record. With the bubbler technique it is possible to obtain reliable information for dosages in excess of 10 20 mg min m^3. If an instrument were to compete in sensitivity with the bubbler method, it would have to have a sensitivity significantly greater than 0.1 μg of substance. Probably the greatest advantage of the bubbler technique is its extreme simplicity and reliability. Because of this there is little doubt that so-called total dosage bubbler sampling will continue always to be of paramount importance in field work. In the following sections, the technique of collecting so-called total dosage samples and the precautions that must be observed in this type of sampling will be discussed.

Low versus High Flow Rate Sampling. Prior to the development of methods suitable for the determination of microgram quantities of chemical warfare agents, the use of macroanalytical methods required the collection of rather large amounts of the substance to be determined. Consequently the tendency during this period was to aspirate large quantities of air at high flow rates through the bubbler unit.[13 17,22] The necessity for high flow rate sampling was accentuated by the use of short sampling periods [22] where, only by this means could sufficient sample be collected for satisfactory analysis. It is clear from the previous discussion that in general continuous sampling must be employed if reliable results are to be obtained. Consequently this discussion is limited to continuous sampling over periods of 1 6 hours. Extensive studies at Bushnell [2 14] and elsewhere [4,19,22] have shown that continuous sampling at high flow rates cannot be used under tropical and subtropical conditions even for times as short as 30 minutes. With the availability of methods suitable for the determination of microgram quantities of substance (see Chapter 37) it became clear that it was not necessary to collect large amounts of material in order that accurate analyses could be made. Since the efficiency of the bubbler as a collecting device decreases rapidly with increasing sampling rate, it is apparent that the best sampling method is one in which the flow rate is reduced to as low a value as possible without reducing the reliability of the subsequent analysis of the bubbler liquid. Under subtropical and tropical conditions it has been found that a flow rate of 0.5 lpm is satisfactory for the sampling of mustard vapor. For less volatile compounds, or where work is being done at lower temperatures, it may be necessary to sample at slightly higher flow rates; it does not seem likely that rates in excess of 2 lpm will ever have to be used.

Developed versus Temporary Sampling Installations. At certain proving grounds, notably at Dugway, Utah, and to some extent at San José, Panama, sampling areas were developed to the extent of providing power lines and vehicles access roads to many points within the sampling area. In a desert location such as that at Dugway, developed target areas are useful provided that a sufficient number of them are available so that a reasonable rotation scheme can be adopted for their use with persistent agents. However, desert areas are of limited interest and the advantages and disadvantages of developed sampling installations in areas of more varied topography should be considered. Development of target areas, particularly in rugged terrain, requires a large expenditure of funds and manpower and in many cases so alters the topography that environmental effects are obscured. Furthermore, in forested area defoliation by mustard vapor becomes a serious factor. In general it appears to be questionable whether the effort expended in developing an area is worth the limited use that can be obtained from such an area. The other alternative is to restrict development to the construction of primitive access trails and to sample with portable self-contained equipment. With the latter practice alteration of the natural features of the area is minimized, a minimum of effort need be expended, and when the area is no longer usable because of defoliation and death of vegetation, a move can readily be made to a new location.

36.2.4 Pump Units

To be useful for field sampling a pumping unit must provide for the aspiration of air through a bubbler at a rate which can be easily controlled and maintained constant to within less than 5 per cent. In addition to the maintenance of a constant flow rate the pump unit should be portable, rugged, and capable of sustained operation. A number of dif-

ferent pump units of varying utility are described below.

Compressed Air Injectors. An air injector type pump was used by all British Empire Stations. This pump which was designed to operate at flow rates of the order of 10 lpm consisted of a compressed air tank, reducing valve, gauges, flow meter, and injector. This type of air pump has few merits and many disadvantages. It requires a heavy multistage compressor unit for recharging, its reliability in operation is low, it is bulky and not particularly portable, it requires considerable servicing, and it is too demanding of attention in the field. Modification of the present design [22] to permit sampling at lower flow rates [51] hardly seems worth while in view of the availability of more reliable pumping units. It should be emphasized that, for efficient and economical operation, manipulations in the field must be kept at a minimum and any device which requires adjustment in the field does not deserve serious consideration particularly if it is to be used in large numbers.

Liquefied Gas Injectors. The use of a readily liquefied gas such as carbon dioxide, propane, or butane instead of compressed air in the operation of an injector type air pump was investigated and a propane-operated stainless steel injector pump was developed.[8,51] Although this pump in principle was superior to the earlier developed compressed air injector pump it still could not be considered the equal of other pumping devices in regard to reliability and ease of operation.

Orifice-Controlled Electrically Operated Pump. It is well-known that flow rates can be controlled within 5 per cent by means of a critical orifice, provided a pressure differential in excess of 0.45 atm is maintained across the orifice. A very satisfactory pump was developed using an electrically driven toy reciprocating steam engine.[13] The pump finally developed had a capacity of from 2 4 lpm at a vacuum greater than 11 inches of mercury and would therefore operate four to eight bubblers at a flow rate regulated at 0.5 lpm by critical orifices.[13] The main advantages of this type of pump are its ruggedness and dependability and the relatively small amount of servicing required for continuous operation over long periods of time. As the orifices remain attached to the bubbler units, operations in the field are confined to turning the pump off and on and determining at the beginning and end of a sampling period whether the pump is capable of producing a vacuum in excess of 0.65 atm. The only disadvantage of importance is that the rather high power consumption requires an extensive storage battery charging set-up. Any sampling method, making use of a critical orifice, however, involves considerable power consumption. The high power consumption and the need for maintaining a reserve supply of storage batteries and extensive recharging facilities does not appear to be too great a price to pay for outstanding reliability, and it must be remembered that one pump can be used to operate four to eight bubblers. If future needs warrant the expenditure of the effort, the design of the pump used for critical orifice operation could probably be improved particularly as far as its weight and volume is concerned.

Constant-Displacement Electrically Operated Pump. A piston-type pump driven by a governor-controlled constant-speed motor was developed [8] in an attempt to provide an air pump of reliable performance and having a minimal power requirement. The actual pump mechanism consists of three cylinders radially placed about the crankshaft, their axes lying in a plane. The three pistons are attached to a single connecting rod bearing on the crankshaft by spring blades which act as connecting rods. The cylinder bores are made in disk-shaped graphite pieces which are free to turn in cast iron holders. As the crankshaft turns and the connecting spring blade is bent, the graphite cylinder block revolves slightly in its holder in response to the forces imposed by the spring. The motion of the cylinder block in the holder shifts the port in the cylinder block back and forth between the intake and exhaust ports in the holder. The three cylinders operate 120 degrees out of phase with one another. This arrangement is not only convenient in design but is also desirable for the production of more uniform flow when all the cylinders are pumping on the same line. This unit was developed too late to permit extensive field tests and it remains to be seen whether this unit is as capable of reliable performance as is the orifice-controlled type of air pump. Until considerable confidence can be placed in the ability of the governor-controlled motor to maintain a constant speed, it might be necessary to provide a device for recording shaft revolutions.

Magnetically Operated Pump. A number of magnetically operated pumps were investigated in attempts to develop pumps of low power requirements. Rubber diaphragm pumps, although used extensively at San José, either are not sufficiently reliable or are of limited capacity. Probably the most satisfactory

SECRET

magnetically operated pump developed was one in which a piston pump constructed from the cylinder of a toy steam engine was driven by a magnet obtained from an electric gong.[3] The pump and battery unit weighed approximately 20 pounds and was capable of continuous operation for 12 hours when delivering air at 1 lpm against a head of 6 cm of mercury. Unfortunately the reliability of operation of this unit was not nearly so great as that obtained with the orifice-controlled pump. The air flow with the former was constant to within ±10 per cent.

36.2.5 Bubblers

Bubbler Design. Careful study of the factors responsible for bubbler efficiency [4,13] has shown that for flow rates of approximately 0.5 lpm or less, very simple bubblers are satisfactory. With increasing flow rates more attention has to be paid to bubbler design in order that equilibrium conditions may be established between the gas and liquid phases. For flow rates of 0.5 lpm or less, the simplest type of bubbler [4,13] is capable of satisfactory performance, and more complicated designs serve only to augment the difficulties associated with charging, discharging, and cleaning the bubblers. For operation with flow rates in excess of 0.5 lpm a number of bubbler designs of varying merit have been suggested.[1,4,11a,b,13,19,22,24,26,30,32,55] A considerable advantage of low flow rate sampling is that it permits the use of an extremely simple bubbler which is easy to manufacture, service, and handle in large quantities.

Bubbler Liquids. Bubbler liquids may be of two basic types, that is, those which do not react with the substance being absorbed and those that do. Diethyl phthalate is an excellent nonreactive solvent for mustard gas [4] and has been used extensively in field work.[13] Diethyl phthalate closely approximates the ideal nonreactive solvent in that its vapor pressure is very low, minimizing losses by evaporation during prolonged sampling periods. It is a very poor solvent for water and thereby can be used under conditions where the water concentration in the atmosphere is high. If a nonreactive solvent is used, and the vapor pressure of the solvent and solute, the ambient temperature, the volume of solvent, and the volume of air passed through the bubbler are known, an accurate prediction can be made of the efficiency of the bubbler unit.[4] Thus, instead of relying upon empirical correction factors which may relate to rather specific situations, one can with confidence predict the performance of the bubbler unit under a variety of conditions. For general application it is important that a solvent be selected that not only will permit the efficient collection of the sample but also will not introduce any complications in subsequent analytical procedures that may be used for determining the amount of substance present in the solvent.[4]

A reactive solvent has obvious advantages provided the rate of reaction between solvent and solute is rapid and the solubility of solute in the solvent is high. Unfortunately a reactive solvent satisfying the above conditions has not been found for mustard gas. Aqueous acetic acid mixtures, notably 50 per cent acetic acid, has been used extensively for the collection of mustard gas.[4,11a,b,13,14,19,22,23,32] Fifty per cent acetic acid suffers from the disadvantage that its composition is altered by aspirating air through the bubbler and, although 50 per cent acetic acid is a fair solvent for mustard gas, the solubility decreases rather rapidly with decreasing concentration of acetic acid. Furthermore it is very difficult to predict with a reasonable degree of accuracy the efficiency of a bubbler charged with 50 per cent acetic acid because of the change in composition of the solvent with time and the rather slow rate of reaction of mustard with aqueous acetic acid.[4] However the efficiency of a bubbler-solvent combination can be determined accurately by experiment for a particular set of conditions. It is important that in practice 50 per cent acetic acid can be used as a solvent to collect mustard gas provided a sampling flow rate of 0.5 lpm or less is used for sampling periods not exceeding 4 hours.[4,13] With higher flow rates serious difficulties are encountered,[4,11a,b,13,14,19,32,34] and in general no adequate solution of the difficulties has been presented. In this connection it has been found [4,13] that should sampling of mustard vapor have to be done for periods exceeding 4 hours or at a flow rate exceeding 0.5 lpm, diethyl phthalate will probably always prove to be a more efficient absorbent than 50 per cent acetic acid.

Solid Adsorbents. The replacement of the liquid bubbler unit by a solid adsorbent presents attractive possibilities. The idea is not a new one since it was used in the period following World War I.[17] It has been found that adsorbents such as silica gel cannot be used generally [4,35] because of the adverse effects of water vapor on the efficiency of adsorption. It is true that charcoal is an excellent adsorbent for mustard gas [4,35] but elution of the hydrolysis products is difficult and incomplete.[4,35] Until an adsorbent can

be found that will permit the quantitative adsorption of mustard gas and subsequent quantitative elution of the hydrolysis products, it does not seem wise to consider replacement of liquid bubbler systems by solid adsorbents.

36.2.6 Miscellaneous

In the preceding paragraphs attention has been called to the more important features of so-called total dosage sampling. Space does not permit giving an account of the detailed operations; this seems hardly to be necessary in view of the fact that an excellent account has already been published.[13] However it does seem worth while to call attention to several special practices of interest to the general problem of determining vapor dosages.

Sampling of Multicomponent Systems. During the course of field work it was desired to sample and determine mustard gas in the presence of chlorine arising from bleaching powder placed on contaminated areas. Since information was not required in regard to concentrations of chlorine, the simplest solution was to provide the bubbler with a suitable filter that would allow the quantitative passage of mustard gas and provide for the quantitative removal of chlorine. Two such filters — one containing pumice granules impregnated with sodium thiosulfate [21] and the other pumice granules impregnated with a mixture of lead acetate and carbonate [36] — have been described. The sampling of multicomponent systems where information must be obtained in regard to all components is usually quite difficult and is possible only in those cases where suitable analytical methods are available for determining the individual components or their reaction products in the presence of each other.[30]

Sampling of Clouds Containing Airborne Droplets. With certain munitions it is necessary to consider the sampling of mustard gas present both as a vapor and a fog. In view of the fact that the droplets present in a fog may pass through a bubbler [23,37] and escape absorption, it may be necessary to place a filter on the bubbler intake that will permit the deposition of the droplets on the surface of the filter and then allow subsequent evaporation of the droplets into the bubbler. Several satisfactory filter devices have been described.[23,30,37] Impingers, although useful in certain instances,[23,27,35,46] have not found extensive use in the sampling of mustard particulates and little is known regarding the reliability of the technique.

36.3 DETERMINATION OF CONCENTRATION VERSUS TIME RELATIONSHIPS

Instruments suitable for the determination of the relation between concentration and time are described in Chapter 38. The method of using these instruments in field work has been described in considerable detail.[13]

36.4 DETERMINATION OF EXTENT AND DEGREE OF LIQUID CONTAMINATION

The extent and degree of *initial* liquid contamination can be determined by adding an easily determinable characterizer to the munition charging.[22,23] The most important characterizers used have been dyes, although in some cases other substances have been used.[2,22,23,26,27,29,32,33,35,44–46,48] The extent and degree of initial contamination can then be determined by visual inspection of the terrain with or without the aid of enameled plates, jump cards, or filter paper assemblies,[12,13,22,23,26,27,29,32,33,35,44–46,48] For reasonably exact work it is obvious that determination of the amount of characterizer on the collecting device by colorimetric means is necessary. In some cases it may be necessary to determine the drop spectrum on the collecting device. Since the distribution of collecting devices in such a way as to insure representative sampling may be difficult or impossible, turf or foliage samples may be taken and the amount of characterizer contained therein determined. The principle disadvantage of the use of characterizers is that it gives information only in regard to initial contamination, or, in cases where liquid droplets have to traverse considerable distances, it gives information only in regard to the situation at the point of droplet formation and not at point of deposition. For this reason it is preferable to use methods which involve actual determination of the substance being studied. Methods for the determination of liquid mustard contamination by actually determining the mustard present have been described.[9,47]

36.5 MISCELLANEOUS METHODS

Attention is called to the bioassay of mustard gas by means of physiological changes in the eyes of

rabbits.[13,18] Although this method is not precise, it served a valuable function in calling attention to the possibility of gross error in chemical sampling procedure.

The determination of the site of bomb-burst or the height of burst is of considerable importance in field work. An instrument was developed [7] to facilitate these operations.

Chapter 37

QUANTITATIVE DETERMINATION OF CERTAIN CHEMICAL WARFARE AGENTS

By *Carl Niemann*

37.1 INTRODUCTION

In the course of the war it became necessary to have at hand reliable methods for the quantitative determination of certain chemical warfare agents. To satisfy this need intensive studies were undertaken not only to determine the reliability and usefulness of existing methods [32,33,66,48] but also to develop new and more sensitive ones.

37.2 DETERMINATION OF MUSTARD GAS

The importance of mustard gas as a chemical warfare agent led to extensive studies on the quantitative determination of this substance. The advantages and disadvantages of the various methods studied or developed are discussed below.

Bromine Titration. Mustard gas, thiodiglycol, or in fact any simple organic sulfide can be determined by titration with an aqueous solution of bromine using methyl red as an indicator.[1] The titration depends upon the rapid bromination of the sulfide to form the dibromide which subsequently hydrolyzes to the sulfoxide. After all the sulfide has been transformed into the dibromide or sulfoxide, the next added increment of bromine oxidizes the indicator to a colorless compound. This method has seen extensive use both in this country and abroad [11,31,69,75,79] and provided that its limitations are recognized has much to commend it. The method is applicable to the analysis of solutions of mustard or thiodiglycol in water, dilute sulfuric or hydrochloric acid, and aqueous acetic acid.[1,11,31,69,75,79] It is simple, rapid, and sensitive, and in the hands of an experienced analyst it gives reliable results. Its principal disadvantage is its lack of specificity [11,31,69] and in practice its use should be limited to those instances where it is certain that no interfering substances will be present in significant amount. The instability of the reagent makes necessary frequent standardization. However, in practice where a large number of determinations are involved, the need of frequent standardization was not found to be a burden.[11]

Hypochlorite Titration. Mustard gas can be determined by titration with standard sodium hypochlorite solution using methyl red as an indicator.[3] The accuracy and sensitivity of this method is comparable to that of the bromine titration and the reagent is somewhat more stable. However, it also suffers from a lack of specificity and its advantages over the bromine titration are questionable.

Chloramine-T Titrations. An aqueous solution of chloramine-T may be used to titrate mustard or thiodiglycol either in the presence or absence of bromide ion. Methyl red is used as an indicator.[18] In the presence of bromide ion the chloramine-T merely serves to oxidize bromide ion to bromine, which then reacts with the sulfur atom as described above. In the absence of bromide ion the reaction takes a different course and twice the amount of chloramine-T is consumed. Apparently chlorination of a carbon atom occurs. These methods were studied in the hope that dilute aqueous solutions of chloramine-T would be stable; however, this was not found to be true.

Dichloramine-T Titration. Mustard dissolved in cyclohexane or purified kerosene may be determined by adding a known quantity of dichloramine-T and titrating the excess dichloramine-T with thiosulfate after the addition of iodide and acetic acid.[29a] A variation of this method dependent upon the sensitizing action of mustard on the reaction between dichloramine-T and cyclohexanol has also been described.[29b,c] These methods, although useful in certain cases, lack the simplicity of more direct methods and for that reason were not generally used.

Chloramine-T–o-Tolidine Colorimetric Method. In this method mustard gas or thiodiglycol dissolved in aqueous acetic acid is allowed to react with a known excess of chloramine-T and the excess reagent estimated colorimetrically [11,19,31,47,64,69,74] through the use of *o*-tolidine. The modification of this method described by the California Institute of Technology group [19] is probably the most reliable. This method in its most desirable form [19] can be used to estimate mustard gas concentrations over the range of 0–100 μg of mustard gas per milliliter of aqueous acetic acid and where the acetic acid concentration varies from

35-50 volume per cent. The method [19] is reliable and sensitive, but its specificity is low, being somewhat comparable to that of the bromine titration. Because this latter method is particularly rapid, the advantages offered by the chloramine-T *o*-tolidine method are questionable.

Iodoplatinate Colorimetric Method. Mustard gas or thiodiglycol in aqueous acetic acid solution reacts with iodoplatinate to form $[(ClCH_2CH_2)_2S]_2PtI_2$ and iodine.[60] The original method [47] based upon the above reaction called for the addition of starch to the reaction mixture presumably to take advantage of the starch iodine color. It should be noted that the iodoplatinate ion is colored and in the presence of mustard gas and starch one is confronted with a diminution of color due to a decrease in concentration of iodoplatinate ion and an increase in color due to the formation of the starch iodine complex. Several attempts [47,73] to improve the original method were not particularly successful so long as starch was added to the reaction mixture. However, if starch was omitted and the method based upon the decrease in color due to a decrease in the concentration of iodoplatinate ion, satisfactory results were obtained.[11,17,21,59,71,73] The modified iodoplatinate procedure [17,21,71,73] gives results which are especially reliable when solutions contain moderate amounts of mustard gas or thiodiglycol; it is sensitive and reasonably specific.[11,31,69] In those cases where it is necessary to analyze aqueous acetic acid solutions of mustard gas or thiodiglycol and where interfering substances are suspected the modified iodoplatinate method [17,21] can be recommended.

β-Napthol Turbidimetric Method. This method [47,74] which depends upon the reaction of an ethanolic solution of mustard gas with an alkaline solution of β-napthol and subsequent estimation of the turbidity produced by the mustard gas β-napthol condensation product, although reasonably specific, is of limited applicability, is far too insensitive, and can be considered to be of only historical interest.

Pyridine Colorimetric Method. The condensation product of mustard gas and pyridine is transformed into a yellow dyestuff upon treatment with alkali. Analytical methods [47,62,69] based upon this reaction, although specific and reasonably sensitive, are of limited applicability.[69] Since other methods of equal or greater specificity and sensitivity are available, its use can not be recommended.

DB-3 Colorimetric Method. The detection of mustard gas through the use of the 4-(*p*-nitrobenzyl)-pyridine (DB-3) reagent has been described in Chapters 34 and 35. This test which is based upon the alkylation of DB-3 by mustard gas and the subsequent formation of a purple dyestuff was used as the basis of a number of colorimetric methods for the estimation of mustard gas. In many of these methods [27,28a,29a,42a,b,55,59] proper attention was not given to important variables and at one time the whole approach was in disrepute. However, careful study [13] of the nature of the reactions and of the important variables led to a method of great utility.[13,31,69] The procedure finally developed [13] involved the use of sodium perchlorate in the condensation reaction in order to augment the sensitivity and specificity of the method, and the effect of *p*H, temperature, concentration of reactants, and interfering substances on the condensation reaction were thoroughly investigated. The development of the colored dyestuff was also studied and the reaction interpreted in terms of the weakly acidic character of the reaction product of DB-3 and mustard gas. Reactions connected with the fading of the dyestuff were studied and it was shown that the principal effect was reaction of the dyestuff with hydroxylic solvents. The method [13] is useful for estimating mustard gas concentrations less than 50 μg ml to within about 1 μg and to within 2 μg for a range of concentration from 50-150 μg ml. In practice the mustard gas vapor is collected in diethyl phthalate, a relatively nonvolatile solvent in which water is not appreciably soluble. The above method is probably the most specific method for mustard gas currently available [11,31,69] and has been adopted for use in a number of establishments [31,62,69] with but minor modification. Its use is strongly recommended particularly in the tropics where diethyl phthalate is far superior to aqueous acetic acid for the collection of mustard gas vapor.

Argentimetric Titration. The Volhard titration of chloride ion arising from the hydrolysis of mustard gas [32,33,47] is too insensitive to warrant further consideration.

Mercurimetric Titration. The mercurimetric titration of chloride ion, arising from the hydrolysis of mustard gas using diphenyl carbazone as an indicator was investigated [19,28c,33,77] and it was found that mercurimetric titration provides a useful procedure for the estimation of mustard gas. Over a concentration range of 0-250 μg of mustard gas per milliliter the concentration can be determined to within 2-4 μg. Since the sensitivity of this method is not so great as others of equal specificity, and be-

cause of the considerable labor involved in carrying out a large number of estimations in this way, the mercurimetric titration has not been used extensively.

p-Nitrobenzyl Bromide Colorimetric Method. This method [46] based upon the condensation of *p*-nitrobenzyl bromide with mustard gas and subsequent treatment of the condensation product with sodium ethoxide to form dyestuff is too involved to warrant further consideration.

Gold Chloride Benzidine Colorimetric Method. In this method [30] advantage is taken of the reaction between gold chloride and mustard gas to give a complex soluble in benzene or monochlorobenzene. The solution of the complex is treated with benzidine to give a blue dyestuff. There is not sufficient information available to comment on the advantages or disadvantages of this method though its reported accuracy is not great (±10 per cent).

Thiosulfate Titration. Thiosulfate ion, as well as many sulfhydryl compounds, reacts with mustard gas in aqueous solution so much more readily than does water that substitution occurs almost to the complete exclusion of hydrolysis. In the proposed method [2] the sample containing mustard gas in a water-miscible solvent such as Cellosolve is added to a known quantity of standard thiosulfate solution (0.01 0.001 *N*) and after the solution has been allowed to stand for 40 minutes, the excess thiosulfate is determined by iodometric titration. This method proved to be of value in certain investigations [2] but unfortunately there is little or no information that would allow one to comment upon its usefulness under more varied conditions.

Iodate Thiosulfate Titration. In this method [55] chloride arising from the hydrolysis of mustard gas is estimated by an iodometric method based upon the metathesis of silver iodate by chloride ion. The method, originally advocated [55] as an accurate method for the determination of mustard, is far too complicated and is surpassed in accuracy and sensitivity by other methods.

Bromate Bromide Thiosulfate Titration. Mustard gas in glacial acetic acid is allowed to react with a known excess of standard bromate bromide solution in the presence of mercuric bromide and sufficient sulfuric acid to make the solution 0.5 *N* in sulfuric acid. After a suitable interval an excess of iodide is added and the liberated iodine titrated with thiosulfate. This method [23b] is a modification of the direct bromine titration and suffers from the same lack of specificity.

Of the sixteen methods described above, five are of such limited applicability that they need not be considered further. These are, the β-naphthol turbidimetric method, the pyridine colorimetric method, the argentimetric titration, the *p*-nitrobenzyl bromide colorimetric method and the iodate thiosulfate titration. The bromine titration, the hypochlorite titration, the chloramine-T titration, the dichloramine-T titration, the chloramine-T *o*-tolidine colorimetric method and the bromate–bromide thiosulfate titration are relatively nonspecific and should be used only in those cases where it is certain that mustard gas is the only reacting component.[11,31,69] Of the methods in this group the bromine titration is the simplest and in the hands of an experienced analyst gives satisfactory results. Of the remaining methods, the DB-3 colorimetric method is clearly superior [11, 21,69] followed closely by the iodoplatinate colorimetric method. The mercurimetric titration has proved to be of value in a number of cases, as has the thiosulfate titration.

The behavior of compounds analagous to or derived from mustard gas in the more important of these methods has been determined [11,31,69] and it can be concluded that adequate methods for the determination of mustard gas are at hand.

37.3 DETERMINATION OF NITROGEN MUSTARDS

The following methods were developed for the quantitative determination of the nitrogen mustards.

DB-3 Colorimetric Method. The DB-3 colorimetric method for the determination of mustard gas [13] can be used without modification for the determination of *tris*(β-chloroethyl)amine (HN3) [13] and with but one minor modification [31] for ethyl-*bis*(β-chloroethyl)-amine (HN1). Presumably the method is equally suitable for the estimation of methyl-*bis*(β-chloroethyl)amine (HN2). The method is sensitive and gives reliable results. Concentrations of HN3 less than 25 μg ml can be estimated with an accuracy of 0.5 μg ml and concentrations between 25 and 75 μg ml with an accuracy of 1.5 μg ml. It is believed that the above method [13,31] is the most satisfactory one available in that most of the other methods using the DB-3 reagent [23b, c, 43, 49, 50, 52] are based upon incomplete study of the reactions involved. The use of BAL to prevent fading of the dyestuff [23b] does not appear to be necessary in the recommended method.[13, 31] Attention is called to two methods depending upon

reaction of the nitrogen mustards with DB-3 impregnated on silica gel, and subsequent development and extraction of the dyestuff with a basic organic solvent mixture[34,35] as an interesting but not very practical modification of the basic method.

Mercurimetric Titration. A moderately rapid routine method depending upon an alkaline hydrolysis of HN3 and the subsequent titration of the liberated chloride ion with standard mercuric nitrate solution using diphenyl carbazone as an indicator has been described.[10] In a 2-ml sample in diethyl phthalate 0.250 μg of HN3 can be estimated to within 2–4 μg. In a 5-ml sample in 0.1 *N* nitric acid 0.500 μg of HN3 can be estimated to within 3–5 μg. Although neither so specific nor so sensitive as the DB-3 colorimetric method, the mercurimetric titration has proved useful.[41]

Base Titration. The titration of an aqueous hydrolysate of HN3 with 0.005 *N* sodium hydroxide has been proposed as a method for the estimation of this compound.[32c] The method is too insensitive for general use.

Acid Titration. The nitrogen mustards dissolved in glacial acetic acid may be titrated with 0.01 *N* perchloric acid in glacial acetic acid using either crystal violet or bromocresol green as an indicator.[32c] Although not particularly sensitive, this method gives reliable results. The necessity of conducting the titrations under anhydrous conditions seriously limits the usefulness of the method.[42]

Of the above methods the DB-3 colorimetric method is by far the most sensitive and specific and has seen extensive use in field work.[31] The mercurimetric titration although less sensitive is of general applicability.[31] The base titration and the acid titration are of limited usability. Attention is called to methods devised for the routine specification analysis of the nitrogen mustards.[50,51]

37.4 DETERMINATION OF CERTAIN ARSENICALS

The only arsenicals of interest as chemical warfare agents are those containing tripositive arsenic. Although it is true that much effort was expended on the development of arsenical chemical warfare agents, not one was found to be of sufficient promise to warrant extensive field study. Consequently analytical investigations on this subject were not comprehensive and little effort was expended in the improvement or evaluation of existing methods.[46–48]

Gutzeit Method. This method, originally advocated[48] for the determination of Lewisite was subsequently simplified by elimination of wet-ashing as an intermediate step.[46]

Dichromate Titration. Lewisite or ethyldichlorarsine may be oxidized with dichromate in aqueous sulfuric acid and the excess dichromate determined by titration with ferrous ammonium sulfate using the barium salt of diphenylamine sulfonic acid as an indicator.[5]

Bromine Titration. Arsenicals such as Lewisite and ethyldichlorarsine may be titrated with aqueous bromine using methyl red as an indicator.[1] Lewisite and ethyldichlorarsine each consume 1 mole of bromine per mole of compound.

Hypochlorite Titration. Lewisite and ethyldichlorarsine may be titrated with hypochlorite using methyl red as an indicator.[3] Attention is called to the fact that the tripositive arsenicals consume only 1 mole of either bromine or hypochlorite per mole of compound, in contrast to the behavior of mustard gas which consumes 1 mole of bromine and 2 moles of hypochlorite.[3]

Cerimetric Titration. Both ammonium sulfatocerate and perchloratocerate solutions were used in an attempt to devise an analytical procedure for the determination of tripositive arsenicals.[32c] The indicators employed were methyl red and the ferrous-phenanthroline complex. The former is an irreversible indicator while the latter is reversible. With the combinations of ceric compounds and indicators tried, the determinations always gave a large positive error and, in addition, the results were not reproducible. This was apparently due to the oxidation of the organic side chain in the arsenical at a rate too slow to result in quantitative oxidation and too fast to neglect completely, as pure arsenic trioxide could be titrated accurately with sulfatocerate solution using the ferrous phenanthroline indicator.

Iodometric Titration. Many arsenicals can be titrated directly with a standard iodine solution using starch as an internal indicator.[32c] However this is not true of ethyldichlorarsine. It is well known that aqueous alkaline solutions of certain arsenites readily undergo oxidation on exposure to air, and it appeared that this reaction might be minimized by proper control of the *p*H of the solution during titration. A *p*H between 5 and 9 must be employed, since at a *p*H less than 5 the oxidation is incomplete and the rate slow, and at a *p*H greater than 9 some of the iodine is converted into iodate and iodide.[47] Attention has been called[32c] to the practice of adding an excess of

standard iodine solution to the tripositive arsenical dissolved in bicarbonate buffer and then titrating the excess iodine with standard thiosulfate. It is known that the use of thiosulfate for titrating small quantities of iodine in a neutral or slightly alkaline solution usually gives erroneous results because part of the thiosulfate is oxidized to sulfate instead of tetrathionate. Therefore standard arsenite solution must be used in place of thiosulfate if accurate results are to be obtained.[23a]

Argentimetric Titration. The Volhard titration of chloride arising from the hydrolysis of lewisite and mustard gas has been proposed along with the estimation of arsenic as a method for determining mustard gas and lewisite when simultaneously present.[26] This method is lacking in sensitivity.

Attention is called to methods proposed for the specification analysis of Lewisite.[40]

37.5 DETERMINATION OF CERTAIN ORGANIC FLUORINE COMPOUNDS

Practically all of the methods devised for the determination of fluorine-containing chemical warfare agents were dependent upon decomposition of the compound in question with concomitant formation of fluoride ion and subsequent estimation of this latter substance. Since satisfactory methods for the determination of fluoride ion were available at the time this work was initiated, the problem was to develop suitable methods for converting the fluorine contained in certain organic compounds into fluoride ion. This is not a difficult problem where several milligrams of the isolated substance are available, but in most cases it was necessary to consider the analysis of very much smaller quantities and their collection from the atmosphere. The various methods proposed for the decomposition of organic fluorine compounds with the formation of fluoride ion are described below.

Ammonia Decomposition. Methyl fluoroacetate collected in aqueous ammonia can be hydrolyzed to methyl alcohol, glycollic acid and fluoride ion by heating the ammoniacal solution in a sealed tube at 150 C, or at a pressure of 4 atm, for 2 hours.[37] A portion of the hydrolysate containing not more than 50 μg of fluoride ion is freed of ammonia by evaporation and the fluoride ion determined by titration with thorium nitrate using as an indicator Brilliant Solochrome Blue, which forms a lake with thorium ion.[38] This method permits the estimation of from 1–100 μg of fluoride ion with an accuracy of about 0.5 μg.[38] This method has been shown to be applicable to the collection and decomposition of dialkyl fluorophosphates[38] and an alternative method of determining fluoride ion involving formation of lead chlorofluoride has been described.[39,41] This latter method is not so sensitive as the thorium titration.

Sodium Decomposition. A procedure was developed for the estimation of fluorine in compounds such as methyl fluoroacetate and β-fluoroethanol in which the compound dissolved in *n*-hexanol was refluxed with sodium, the fluoride ion extracted with water and the fluoride ion in the aqueous phase titrated with thorium nitrate using sodium alizarin sulfonate as an indicator.[7] In the hope of enhancing the color change at the end point of the thorium nitrate titration, 54 dyestuffs used individually in conjunction with sodium alizarin sulfonate were investigated. Only du Pont Azo Blue appeared to be of value.[7] Comparison of Solochrome Brilliant Blue with sodium alizarin sulfonate revealed that each indicator had some advantages depending upon the concentration of fluoride ion. The former indicator was found to be more sensitive at lower concentrations of fluoride ion.[7,38] A colorimetric method for the estimation of fluoride ion based upon the bleaching of the thorium-alizarin sulfonate lake has also been described.[8] The decomposition of organic fluorine in ethanol solution by sodium and subsequent estimation of fluoride ion,[36b] although useful in certain cases, is not so generally useful as is the method using a higher boiling alcohol.[7]

Sodium Peroxide Decomposition. Methods dependent upon fusion of an organic fluorine compound with sodium peroxide[6a,b,c] or with metallic sodium[5,6a,b,c,64b] to give fluoride ion are of interest only in the analysis of compounds obtainable in an isolated state.

Pyrolytic Decomposition. Methods based upon the pyrolysis of organic fluorine compounds either in the presence[20] or absence of hydrogen[65,d] although successful in some instances do not appear to be generally useful, and in many cases quantitative conversion into fluoride ion is not obtained.[20,65c,d] This is particularly true of the method based upon combustion of an aqueous ethanol solution of the fluorine-containing compound.[26a,b,c,71]

Periodate Perchlorate Decomposition. Organic fluorine compounds such as methyl fluoroacetate, *p*-fluoroethanol and the fluorophosphates in aqueous solution can be oxidized or hydrolyzed to give fluoride ion

by treatment with a mixture of potassium metaperiodate, silver perchlorate, and perchloric acid.[15] The reaction mixture is refluxed and then distilled at 135–145°C, maintaining the temperature at the above value by the addition of water until 100 ml of distillate has been collected. An aliquot portion of the distillate is then analyzed for fluoride ion by titration with thorium nitrate solution using Solochrome Brilliant Blue as an indicator.[15]

The chemical warfare agents such as the fluoroacetates and their homologs, never showed sufficient promise to justify extensive field testing. Consequently there was no opportunity to evaluate critically the usefulness of these methods under varying conditions. It should be pointed out that in certain instances it was possible to devise a fairly specific method for a fluorine-containing compound. For example, S_2F_{10} can be determined in the presence of SF_4, SO_2F_2, NO_2, N_2O and SF_6 by removing the latter gases by passage through a bubbler charged with alkali and then passing the effluent stream through a bubbler containing a solution of sodium or potassium iodide in acetone, the iodine liberated being determined by titration with thiosulfate.[4,63a]

37.6 MISCELLANEOUS DETERMINATIONS

The analytical methods discussed in this section were not used extensively and little information is available in respect to their usefulness and reliability.

Determination of Alkyl Fluorophosphates. The alkyl fluorophosphates can be hydrolyzed with ammonia to give fluoride ion as indicated previously. Alkaline hydrolysis ordinarily does not result in the formation of phosphate ion. Alkyl fluorophosphates collected in aqueous alkali can be hydrolyzed by either hydrobromic or hydroiodic acid to give phosphate ion which can then be determined by colorimetric methods involving the formation of molybdenum blue.[37,58,64]

Determination of Hydrogen Cyanide. A determination of hydrogen cyanide was made in the presence of titanium tetrachloride, chlorosulfonic acid and it was found that hydrogen cyanide collected in a bubbler charged with 0.25 *N* sodium hydroxide can be determined either by titration with silver nitrate or by a colorimetric method based upon the reaction of cyanide ion with picric acid.[22] In the former method aliquot portions of the aqueous cyanide solution were titrated with silver nitrate to a silver iodide end point after making the solution 0.6 *N* in ammonia. The hydroxyl ion concentration can vary between 0.5 and 1.5 *N* without materially affecting the results. The precision of the method is ±10 μg from 50–1,000 μg and ±20 μg from 1,000–10,000 μg. The presence of 100 mg of sodium sulfate, sodium chloride, potassium cyanate, sodium formate, or sodium sulfite is without effect upon the titration. The picric acid colorimetric method may be used for determining 2–100 μg of cyanide ion with an accuracy of ±2 μg. Chloride, sulfate, cyanate, formate and ammonia ions do not interfere, but sulfite ion does.

Determination of Ethyl Dimethylamidocyanophosphate (MCE). MCE collected in aqueous sodium hydroxide hydrolyzes to form cyanide ion which can be determined by titration with silver nitrate as just described.[25a] To determine the phosphorus in MCE as phosphate ion it was found necessary to resort to fuming with perchloric acid [61] or oxidation with both alkaline and acid permanganate.[25b]

Determination of Chloroacetophenone (CN). Chloroacetophenone collected in diethyl phthalate may be estimated colorimetrically with the aid of *m*-dinitrobenzene.[30]

Miscellaneous Determinations. Attention is called to methods developed for the specification analysis of both hydrogen cyanide [14] and cyanogen chloride,[9,12,15,21] the determination of certain chemical warfare agents in contaminated carbon clothing,[48] and the determination of certain chemical warfare agents in contaminated foodstuffs.[20,61]

Chapter 38

INSTRUMENTAL METHODS FOR DETERMINATION OF CERTAIN CHEMICAL WARFARE AGENTS

By *Carl Niemann*

38.1 INTRODUCTION

IN CHAPTER 37, methods for the determination of certain chemical warfare agents using so-called classical chemical techniques were described. As indicated previously, the determination of mustard gas was by far the most important problem. Although certain of the so-called classical methods were reliable and were used extensively [28,31,32,38] there always existed a need for new and improved methods of analysis. In the laboratory the lack of skilled analysts, the primitive facilities, and the necessity of conducting thousands of individual analyses emphasized the need for reliable and rapid instrumental methods of analysis. If chamber experiments were to give a maximum amount of information, it was necessary to develop instrumental methods that would furnish data which either was unobtainable by classical methods, or could be obtained only with considerable difficulty. Finally there was an urgent demand for instrumental methods of analysis that could be used in the field and that would give information otherwise unobtainable. The instrumental methods of analysis described below relate primarily to the determination of mustard gas and only incidentally to the determination of other chemical warfare agents.

38.2 SEMIAUTOMATIC AND AUTOMATIC TITRIMETERS

The discovery that mustard gas as well as a number of other chemical warfare agents could be titrated potentiometrically [1] was of inestimable value in the development of instrumental methods for the analysis of these chemical warfare agents. In the original investigation it was shown [1] that mustard gas and certain arsenicals could be titrated in dilute sulfuric acid solution with bromine and other oxidizing agents using two platinum electrodes and a sensitive galvanometer to determine the end point. Although the original method [1] is now of historical interest, it served to demonstrate the potentialities of the approach.

38.2.1 Semiautomatic Titrimeter [4]

In the usual methods of potentiometric titration,[27] the substance to be titrated is added to a half cell containing a suitable electrode and connected to another half cell containing a reference electrode. The reagent is added in increments and the potential is measured after each addition by means of a potentiometer. The potential is then plotted against the volume of reagent added and the end point determined from the plot. This method is accurate and sensitive but does not readily lend itself to instrumental development. The apparatus herein described is based upon the fact that in many cases the increase in potential at the end of the titration is so great that it is not necessary to measure the increase quantitatively, and instead of a potentiometer only a galvanometer is required. This will be recognized as the principle of the so-called Pinkhof titration. A reference electrode is used which has the same potential as that of the titrating electrode at the end point of the titration. The titrating electrode and the reference electrode are connected to a galvanometer and the reagent slowly added until a sudden deflection, or in some cases a null point reading, is observed on the galvanometer. This is taken as the end point. In the apparatus under discussion the volume of reagent added is not read directly but is determined by measuring the time a constant flow-type burette [38] is open.

The apparatus [4] consists of a storage battery, an air pump, a titration cell, an electrically operated constant-flow-type burette, a galvanometer, and a switch. The galvanometer and switch may be located wherever the operator wishes to be. Four wires connect the two units. In operation, air containing the substance to be determined is drawn through the titration cell at a constant flow rate. After a selected time interval, depending upon the concentration of the substance to be determined in the airstream, the switch is closed, thus opening the constant flow-type burette. The circuit is allowed to remain closed until the galvanometer needle is deflected a selected number of scale divisions. At this time the switch is again

opened, thus stopping the flow from the burette. The time interval from the beginning of the aspiration of gas through the titration cell to the end of the titration is directly proportional to the amount of air passed through the cell, and the time interval from the beginning of the titration to the end of the titration is directly proportional to the amount of reagent added. Since the flow rate of the air through the cell and the strength of the reagent is known, the quantity of the substance to be determined in the airstream can be readily calculated. If the substance to be determined is in solution, a known volume of the solution can be added to the titration cell and the titration performed as described above.

The above apparatus,[4] or a simplified version of it in which the electrically operated burette is replaced by a manually operated one,[6] has been used for the determination of mustard gas, its homologs, and certain arsenicals, all of which may be titrated potentiometrically with bromine or other oxidizing agents.[4,6,28] Phosgene, hydrogen cyanide, chloropicrin, and other substances which liberate chloride ion in the presence of water or form insoluble compounds with silver ion may be titrated potentiometrically with silver nitrate using a silver silver chloride electrode. In the case of phosgene it is necessary to have solid *p*-chloroaniline in the titration cell to insure complete hydrolysis.[6] The nitrogen mustards can be determined potentiometrically by titration with silver nitrate,[6,9] with dilute nitric acid using a quinhydrone electrode,[6] and with dilute sodium hydroxide using a quinhydrone electrode after pyrolysis of the gases entering the titration cell.[13] The semiautomatic titrimeter and its simplified version were used extensively for the determination of mustard gas present both as a gas[4,6] and in solution.[6] The apparatus proved to be quite sensitive, in that a fraction of a microgram of mustard gas could be detected, and it was sufficiently precise for most purposes. Unfortunately, since it is dependent upon the use of the bromine titration for the determination of mustard gas, its specificity is not great. The use of an electronic amplifier and a milliammeter in place of the less robust galvanometer has been suggested.[2,22]

38.2.2 Field Model Semiautomatic Titrimeter

The need for a titrimeter capable of being operated in the field led to the development of an instrument, under the joint auspices of the Chemical Warfare Service [CWS] and the National Defense Research Committee [NDRC], Division 9, based upon the semiautomatic titrimeter described above. The field model was modified during the construction of several hundred units and only the final modification[28] will be discussed. The instrument has four functional parts: a titration cabinet, a portable 6-volt wet-cell battery, a five-wire cable on a reel, and a control box. The titration cabinet contains an electrically driven air pump, a titration cell, an electrically actuated constant flow-type burette, an overflow trap, an electric relay box, and a three-way magnetic valve. The principal innovation introduced into the field model titrimeter was the provision for the stirring of the titration cell with clean air. This was found to be necessary because, if high concentrations of mustard gas were present in the atmosphere, continued aspiration of the contaminated air through the titration cell during the titration period did not permit the attainment of an end point within a reasonable time. It should be pointed out that it is not practical to change the concentration of the reagent at frequent intervals under field conditions. With the aid of a three-way magnetic valve it was possible to aspirate contaminated air through the titration cell for a selected collection period, and then, by diverting the airstream through a charcoal trap, to pass clean air through the cell during the titration period. The control box contains a galvanometer, two variable resistances, a stopwatch, suitable toggle switches to control the pump motor, and the burette valve and magnetic three-way valve. The control box is attached either directly to the titration cabinet or indirectly by means of a cable.

Although several hundred field model semiautomatic titrimeters were used in field work both in this country and abroad and were responsible for obtaining much valuable data, their operation required the services of a large group of people. The fact that the instrument and its accessories were unwieldly and heavy added to the difficulties inherent in operating on difficult terrain. In addition, extensive servicing was required. Under more favorable conditions it may be possible to provide for better instrumentation with particular regard for lighter and less bulky equipment and tropic- and dustproofing of all electrical and mechanical components. Such a program would be justified only if the instruments were to be used for the determination of chemical warfare agents other than mustard gas

because other and more satisfactory instruments have been developed for the determination of that substance.

38.2.3 Electrolytic Semiautomatic Titrimeter

In the above instruments the reagent is added to the titration cells by means of an electrically or manually operated burette. An alternative and superior method of introducing the reagent into the titration cell was discovered in 1944.[33,34] This new method was based upon the electrolytic formation of the reagent in the titration cell. In principle four electrodes are mounted in the titration cell, two serving as observing electrodes and two as generating electrodes. The solution in the titration cell contains an electrolyte which can be converted into the reagent by electrolysis. In carrying out a titration the sample is introduced into the titration cell and current is passed at a constant rate through the generating electrodes until the end point is observed through the use of the indicating electrodes and a suitable galvanometer. Since both the time the current is passed through the generating electrodes and the intensity of the current are readily determinable quantities, the amount of reagent liberated in the titration cell and the amount of substance titrated are readily calculated. The advantages of electrolytic generation of the reagent are manifold in that it eliminates the need for the burette assembly which is fragile and bulky, does not require standardized reagent solutions, permits the use of any convenient concentration thereby allowing the apparatus to function over a wide range of sample concentrations, and, finally, opens the way to more general and automatic instrumentation.

The above principle has been applied in the construction of several instruments for the electrometric titration of mustard gas.[35,36] In one of these[36] one pair of platinum electrodes is used to electrolyze a solution 0.2 *N* in sulfuric acid containing 0.1 per cent potassium bromide. A similar pair connected to a separate current source is used to determine the end point. A potential difference of 0.2 volt across the indicating electrodes rapidly polarizes them and thus no current flows until the end point when the excess bromine depolarizes the cathodes. The electrolyzing potential is maintained at about 1.5 volts, thus being between the decomposition voltages of potassium bromide and sulfuric acid, 1.25 volts and 1.78 volts respectively. The other instrument[35] differed only in minor detail but different operating conditions were employed.

An interesting application of the electrolysis principle is to be found in an apparatus devised for the titration of acid gases by electrolytic generation of hydroxyl ion.[37] In this apparatus a double-compartment cell is employed.

38.2.4 Field Model Electrolytic Semiautomatic Titrimeter

The instruments described in the preceding paragraphs were designed primarily for laboratory use. In view of the difficulties associated with the operation of the field model semiautomatic titrimeter, steps were undertaken in 1941 by the Bushnell establishment to develop a field model electrolytic semiautomatic titrimeter.

The instrument finally developed[38] consists of a titrimeter, cabinet and cables. The titrimeter cabinet is a lightweight resin bonded plywood box equipped with carrying handles and dust- and moisture-proofed by means of a rubber gasket between the lid and bottom. Chest catches allow the cabinet to be closed tightly. Suitable holes, one-half in the lid and one-half in the bottom, provide the outlets for the intake tube, main cable, and battery cable when the machine is in operation. Rubber bushings in these holes keep tight seals around the intake tube and cables, and plugs are provided for the holes when the machine is not in operation. All the elements within the cabinet are mounted on a removable base panel. These include (1) a motor-operated pump similar to the one in the field model semiautomatic titrimeter, (2) the cell, which is held in a block and which contains two platinum generating electrodes in addition to the indicating electrodes, (3) an overflow trap of simple bubbler tube construction, (4) a relay housed in glass to control the motor, and (5) a brass plate on which is mounted the amphenol connector for the main cable and a toggle switch to control the motor relay. The control box contains (1) a milliammeter reading from 0-2 and 0-20 ma, (2) a double-pole, double-throw switch to select these ranges, (3) a galvanometer, (4) a shunt register, (5) a circuit for regulation of the electrolyzing current, and (6) switches to control the electrolyzing and motor relay circuits. The electrolyte contained in the titrating cell is 0.25 *M* in sulfuric acid and 0.1 *M* in potassium bromide. Air containing the agent is bubbled through the titrating cell at the rate of 1 lpm and two polarized platinum electrodes are used as

indicator electrodes. With this instrument it was possible to achieve rates of titration of from 0.82–16 μg of mustard gas per second. This latter value permits estimation of concentrations well above the highest observed in field experiments.

Although this instrument was developed too late to be put to extensive use, it is reasonably clear that it was the most satisfactory semiautomatic field instrument developed. It is possible that the instrumentation could be improved and this might be profitable if future work requires a semiautomatic instrument.

38.2.5 Automatic Titrimeter

An automatic titrimeter was developed [16] which was capable of indicating concentrations of mustard gas, or any other substance reacting with bromine. The response of the instrument to varying concentrations of mustard gas was reasonably rapid so that within limits it was capable of indicating for practical purposes concentrations prevailing at any one time. In this instrument one airstream is passed first through a charcoal trap to remove any substance reacting with bromine, then through a needle valve, and then through a solution of bromine in potassium bromide. The airstream containing a definite amount of bromine is then passed through a length of capillary tubing, through a T-tube, and into a cell containing a platinum electrode and a reference electrode. The two electrodes are connected through a variable resistance to a 0–50 microammeter. A second airstream enters the system at a known rate through a tube containing a by-pass equipped with a second charcoal trap, passes through a length of capillary tubing, and then joins the bromine-laden airstream at a T, the two streams entering the titration cell together. The instrument is provided with an electrically driven air pump and a miniature storage battery.

In operation, the second or sampling airstream is first by-passed through a charcoal trap, thus leaving pure air to mix with the bromine-containing stream at the T. The needle valve on the airstream passing through the bromide saturator is adjusted so that a reading of, say, 45 μa is observed on the microammeter. This operation provides for the adjustment of the instrument to an arbitrary zero reading. The sampling airstream is then diverted from the by-pass and its trap and is allowed to mix with the bromine-laden airstream. If mustard gas or any other substance which reacts with bromine is present, an amount of bromine equivalent to the amount of substance present is removed from the combined airstreams and cell, and the current read on the microammeter will decrease in direct proportion to the amount of substance present at that time. The instrument constructed [16] was suitable for the determination of mustard gas concentrations varying from 0–10 μg/l or from 0–100 μg/l by suitable adjustment of the resistor in series with the cell and meter, and from 0–500 μg/l by changing the capillary in the sampling airstream to lower the rate of air intake. It is clear that the instrument requires calibration against known concentrations of the substance to be determined. The accuracy obtainable may be about ±10 per cent. It should be emphasized that comparison between the results obtained by this instrument and those by other means under actual field conditions is rendered very difficult by the fact that only by integration of many concentration-time values to give a total dosage can any comparison be made at all. Such a series of concentration readings is obtained only by continuous observation of the instrument over a relatively long time period by an operator exposed to the same concentration of mustard vapor as is the instrument itself. This undesirable feature in the instrument's use was chiefly responsible for its being used only very slightly in field tests. The important observation made in connection with its limited use in the field was that the zero point setting was far too unsteady. Electrolytic generation of bromine, as pointed out below, would probably improve this undesirable feature in the instrument's operation. The instrument is compact and portable and appears to offer considerable promise. The instrumentation is primitive and there is little doubt that with proper care in respect to instrumentation detail an instrument could be constructed that would be quite useful for the determination of so-called instantaneous concentrations. The basic principles embodied in the instrument seem to be excellent ones and worthy of further development. Such development should consider, aside from features of convenience, the possibility of improving the indicating system so as to lessen the amount of current drawn through the cell and of improving the design of the titration cell so as to minimize loss of bromine in order that electrolytic generation of bromine could be used generally. With the present design, electrolytic generation of bromine is possible for concentrations in the 0- to 10-μg range.[16] Aside from eliminating the need of a separate solution as a

source of bromine, electrolytic generation of the reagent would possibly obviate the need for calibration.

38.2.6 Automatic Recording Titrimeter

An automatic recording titrimeter was developed[5,8,12] which was based upon the use of the semiautomatic titrimeter described in Section 32.2.1. This automatic instrument, which contains an electrically operated, constant flow-type burette and a photoelectric relay consists of a titration and a recording unit. Air is drawn into a cell contained in the titration unit, where the titration is automatically effected. The recording unit controls the automatic titration in the titration unit and records the analysis on a chart. The titration proceeds as follows: Air containing the substance to be determined is drawn continuously at a constant known rate through a solution which absorbs the substance and which contains an electrode which detects indirectly the presence of the substance. A reference electrode of approximately the same potential as the end point potential of the first electrode completes the electrolytic cell. The potential of this cell controls, through a photoelectric relay, the addition of titrating liquid to the cell. When the potential of the cell is approximately zero, no titrating liquid enters. When the substance to be determined is present, producing a change in potential, titrating liquid enters the cell at a constant rate until the substance to be determined is no longer present. Thus a state of electrical balance is produced in the cell. Periodically, addition of titrating liquid is stopped and the substance allowed to accumulate in the cell. At the end of this sampling period, titration begins and proceeds until the substance to be determined is no longer present. The amount of substance which enters the cell during the sampling and titrating periods can be calculated from the amount of titrating liquid which enters the cell during the titration period. Since the rate of flow of titrating liquid into the cell is constant, time of flow is proportional to the quantity of reagent entering the cell. The recorder marks the duration of titration and nontitration periods and thus provides the necessary information for calculating the concentration of substance to be determined in the incoming air. Two titrating solutions were used,[5,8,12] one containing silver nitrate and the other containing bromine, depending upon the type of substance to be determined. A silver electrode was used with the silver nitrate reagent and a platinum electrode with the bromine reagent. The bromine titration will determine 0.10–10,000 μg of mustard gas per liter of air. The silver nitrate titration is slightly less sensitive. In the determination of low concentrations of mustard gas, the air may be passed over certain kinds of soda lime to remove any vapors of the polysulfides of mustard gas which may be present.[17] The overall accuracy of the instrument is about ±10 per cent. The recorder may be at any desired distance from the titration cell and several titration cells at various locations may be operated and recorded consecutively by the same recorder.

A simple electronic timing circuit for use with the above automatic recording titrimeter was devised.[10] It made possible the selection of time cycles varying between 0.25 and 5.8 minutes and thus worked below the lower limit of 3 minutes permitted by the gear system of the unmodified titrimeter. It also arranged automatically for the start of a new sampling period directly after the preceding period is completed.

Six automatic recording titrimeters were constructed[8] and were used either as constructed or with minor modifications[20] primarily in chamber experiments where their performance was reasonably satisfactory.[10,20a,b,c,20] Use of the above type of automatic recording titrimeter is limited to the laboratory or semipermanent installations. It is definitely not a portable instrument and it is certain that it could not survive field usage. It is very questionable that further instrumentation along the above lines would result in a usable portable instrument because of the fragility and bulkiness of a number of components necessary for this type of instrument. A stronger reason for not continuing development along the above lines is that another instrument based upon different principles and offering considerably greater promise has already been developed. This is described in the following section.

38.2.7 Automatic Electrolytic Recording Titrimeter

For use in chemical warfare studies and in other problems, an automatic recording titrimeter should provide for (1) the continuous indication of the concentration of the substance to be determined, (2) the [illegible] as it varies, either recording of the [illegible] slowly or rapidly, with time and (3) the continuous indication of the integrated value of the concentration. That is, the instrument should be capable of indicating the concentration at any time, the dosage accumulated from an arbitrary zero time to the time

of reading, and the variation of concentration with time. It is realized that if sufficient time were available and conditions ideal, all of the information could be obtained from the concentration versus time record. However, in field work conditions are rarely if ever ideal and, since time is often an important element in field work which involves exposure of humans to toxic agents, it is extremely desirable to have immediate information in regard to the concentration at any one time and the dosage accumulated during a given time interval.

An automatic recording electrolytic titrimeter was developed [2] to satisfy not only these requirements but also others relating to portability and sustained unattended operation. It was intended that the instrument be used primarily for the determination of mustard gas. The complete instrument consists of (1) the titration unit, (2) the recording unit, (3) an auxiliary integrating unit, and (4) an auxiliary power unit. The titration unit contains a titration cell utilizing electrolytic generation of the titrating agent, an electronic power amplifier operated on dry cells, a motor-driven air pump operated by a storage battery also in the unit, a panel meter for indicating concentration, a gas-type integrator for indicating dosage (concentration × time) values, the necessary controls for the adjustment and operation of the instrument, and electric outlets for connection with the other units. The recording unit was simply a commercial model ink-recording milliammeter. The auxiliary integrating unit is an electronic device developed subsequent to the gas-type integrator. The electronic integrating device is capable of greater precision and utility than the gas-type integrator but is somewhat larger. The auxiliary power unit is provided for those cases where long periods of operation are required.

The way in which the titrimeter operates is illustrated in Figure 1. Although the several steps involved in the operation occur simultaneously, it is convenient to arrange them in a hypothetical sequence as follows: (1) When no mustard is being absorbed by the titration cell, the generating electrodes produce bromine at a low constant rate to provide a constant but very small bromine concentration in the cell. (2) The observing electrode system (platinum and calomel) is very sensitive to small changes in the bromine concentration. When mustard is absorbed in the cell, it reacts quantitatively with the bromine and produces a change in the potential of the observing electrodes. (3) The "observed potential" is applied to the input terminals of an electronic power amplifier, the output terminals of which are connected in series to the generating electrodes and the output current meters. (4) The change in the "observed potential" causes a change in the bromine-generating current which is just sufficient to compensate for the consumption of bromine by the absorbed mustard. The power amplification of the amplifier is sufficient to produce large current changes for very small changes in the observed potential. For this reason the initial bromine excess is almost completely restored. (5) Since the change in the bromine-generating current is a direct measure of the change in the rate of consumption of bromine by mustard, the record of the current may be used as a record of mustard concentration, the proportionality factor being given by Faraday's law. The sampling flow rate is constant, conveniently at 1 lpm.

Equilibrium concentrations are set up in the titration cell despite the constant addition of the reactants because of the circulation of liquid through the cell and the aeration of bromine by the airstream. Circulation is of great importance in the rapid attainment of equilibrium and in the prevention of hunting in the instrument. The absorbing solution is cleansed of excess reactants and reaction products by passage through a bed of granular charcoal.

For observing the "instantaneous" concentration of mustard gas, a 0–1 milliammeter in the generating current circuit was employed. Per minute, one ma generates the quantity of bromide which reacts with 19.5 μg of mustard. Since the air sampling flow rate is 1 lpm, a meter reading of 1 ma corresponds to 50 μg of mustard gas per liter to within 1 per cent. The meter sensitivity can also be decreased to 100 μg of mustard gas per liter full-scale by inserting, with the aid of a toggle switch, a shunt resistor in parallel with the meter when a greater range is desired. The recording unit may also be placed in the generating current circuit, thereby enabling the recording of the concentration as a function of time. For determining the integrated value of the concentration over a given time interval two devices were developed, one of which is a simple electrolytic gas generator and the other an electronic circuit and impulse counter. Both may be placed in the generating current circuit. The electrolytic gas-type integrator, which was based upon the displacement of a dyed solution along a helical path by gas generated from two small electrodes, is graduated in units of 2 ma-min, corre-

sponding closely to 100 μg of mustard. The range of the integrator extends to 10,000 μg of mustard.

The electronic current integrator, or microcoulometer, can be attached to the titrimeter in place of the gas-type integrator or in series with it. The clock-type counter dial of the microcoulometer permits the direct reading of the instantaneous value of the integrated concentration. The microcoulometer can also be used with the titrimeter to perform very rapid automatic titrations of microgram samples of mustard. In one series of titrations, only 15 seconds were required for the completion of each titration, including the adding of the sample and the recording of the result.

It is believed that in principle the above instrument is vastly superior to all others developed for the instrumental determination of mustard gas and other substances determinable by a reagent capable of being formed by electrolysis. Further instrumentation is needed to produce an instrument that will withstand the vicissitudes of field work not only in the tropics but also in temperate zones. If such an instrument could be produced and demonstrated to be reliable under a variety of operating conditions, it would be an exceedingly valuable instrument for all types of problems including some not pertaining to chemical warfare.

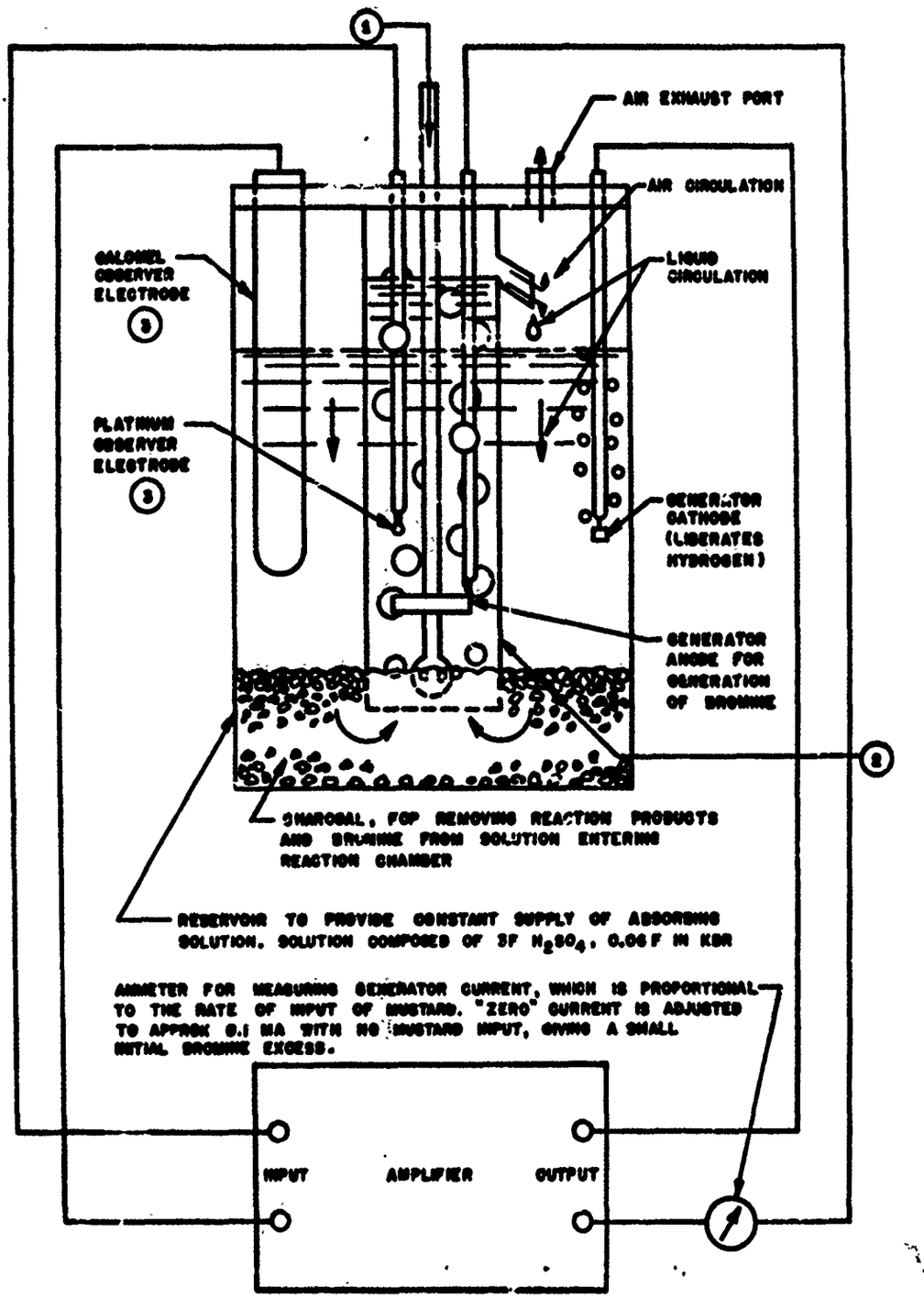
38.3 AUTOMATIC TAPE RECORDERS

Tape recorders are instruments which in principle depend upon reaction of the substance to be determined, or a product thereof, with a tape impregnated with a reagent, the product of this reaction being a color or stain whose intensity, or extent, is proportional to the concentration of the substance to be determined. The exposure of successive segments of the tape to the substance to be determined is achieved by mechanical means. In this way a record is produced which can be read, with or without the aid of auxiliary equipment, to give information regarding the average concentration of the substance to be determined over the sampling time interval and the variation of this incremental average concentration with time.

38.3.1 Paper Tape Recorder

A paper tape recorder and auxiliary equipment was developed [18,21,22a,b] and produced in sufficient quantity to permit evaluation of this type of instrument under a variety of field conditions.[18,21,22a,b] The paper tape recorder is contained in an aluminum case containing two compartments, the lower providing space for a small 6-volt storage battery and the upper one for the sampling and recording mechanism. The instrument fully assembled weighs 25 pounds. Air containing the substance to be determined is drawn into the sampling and recording mechanism through a metal tube, equipped with a rainproof cap, projecting through the top of the case. No special provision is made for air exhaust as there is sufficient leakage at the on-off switch and at other points for the escape of air. The sampling and recording mechanism is driven by a 6-volt shunt-wound motor with built-in worm gear. The suction pump is an automobile windshield wiper motor from which the valve mechanism has been removed and which is provided instead with a set of Bunsen check valves connected with fittings attached to the two pump cylinders. The suction pump is driven by means of a connecting rod and crank. The volume of air pumped is approximately 850 ml/min with the grade of paper usually used. The paper tape transport mechanism can be engaged either intermittently or continuously. The paper tape transport mechanism consists of a pair of intermittent spur gears driving a standard 16-mm film sprocket, and two cams, one of which controls a valve on the intake air line, the other releasing the paper during its period of travel. As usually used in sampling persistent agents, the paper tape is moved so that every other frame on the resulting record is unexposed. This gives as many blanks for photometry as there are exposed frames. The provision for tape feed and rewind is conventional for 16-mm motion picture equipment. An actuating cam was designed so as to be readily replaceable in order to provide wide latitude in the choice of exposures when working with different agents. The rate of paper travel is normally that which produces one exposure per minute. With suitable modifications the paper tape travel can be changed to a multiple or fraction of this rate, thus providing for greater sensitivity or greater range of concentration.

The volume of air drawn through the paper when the film-driving mechanism is in continuous operation (i.e., for nonpersistent agents) is governed by the angular extent of the rise on the cam operating the air valve. The volume of air sampled in this way at each exposure is approximately 2 ml. Air entering the intake tube is passed, in order, through a control valve, through the paper tape, through a trap which contains either charcoal or silica gel or both, and



Note 1. Mustard entering in contaminated air stream.
Note 2. Reaction chamber. Mustard is absorbed in the solution, a small excess of bromine being present.
Note 3. Observer electrodes detect potentiometrically changes in the bromine concentration resulting from changes in the rate of addition of mustard. Amplifier regulates the rate of electrolytic generation of bromine, in accordance with Faraday's law, so that the bromine excess is restored.

FIGURE 1. The principle of operation of the automatic titrator.

finally to the suction pump. The suction pump is thus continually discharging clean air within the instrument case. The current consumption is approximately 1.8 amp, the battery capacity thus providing for approximately 10 hours of operation. When used for nonpersistent agents, the limiting factor in the sampling time is the size of the roll of tape. One full role of tape provides for 90 minutes of running time. The paper No. 750 manufactured by the Hulburt Paper Co. was selected as the best for subsequent impregnation, since it meets both the physical and chemical requirements.

The accessory equipment required for the operation of the recording units included: a tape-impregnating machine in which the paper tape is impregnated with reagents appropriate for the substance to be determined; a photometer for determining the intensity of the colored frames; and a portable calibrating unit for producing known vapor concentrations of the substance to be determined. The impregnating apparatus was designed to carry out automatically the impregnation and drying of two strips of tape simultaneously. The paper tapes are passed by means of a motor-driven sprocket from feed reels into a common bath containing an impregnating solution which is fed from a reservoir through a constant level siphon. The tapes travel up and down through a drying tower, through which hot air is circulated, and are then passed onto rewind reels. The apparatus provides for three speeds of tape travel and for two settings of the tower heat.

The photometer assembly consisted of three parts: (1) the frame which carries the light source, tape-feed mechanism, and reels, (2) the photoamplified cartridge which contains the photocell and the vacuum-tube amplifier and (3) the control unit which contains the indicating meter, controls, and dry batteries. Current for the light source, motor, and amplifier tube filament is obtained from auxiliary storage batteries. The photometry is performed by measuring the light transmitted through the paper tape. As the records usually consist of a series of colored spots interspersed at intervals with blank spots, the instrument is adjusted, by means of Polaroid filters, to give a full-scale reading for a blank spot; the tape is moved to place a colored spot in the light path and the decrease in transmitted light is taken to be proportional to the intensity of the stain. A calibration curve was prepared relating intensity of stain to concentration of the substance to be determined.

The portable calibration unit provided for the availability of airstreams containing known amounts of the various chemical warfare agents and was simply a system permitting the controlled dilution of an airstream containing a relatively high and known concentration of the substance to be determined.

Test papers were developed for determining mustard, cyanogen chloride, phosgene, and hydrogen cyanide, and the instrument was used in many field trials involving the use of these agents. When the paper tape recorders were first used in field work, considerable difficulty was encountered in preparing impregnated paper tape that would permit satisfactory performance under varying conditions of temperature and humidity. In practically all if not in all cases, it seemed possible to overcome earlier difficulties, and by late spring of 1945 the tape recorders were being used in field trials. Although more opportunity for comparison of the paper tape recorder, using its now most satisfactory paper for mustard gas, with the field model electrolytic semiautomatic titrimeter would be desirable, it seems that the two instruments may be capable of comparable accuracy. The paper tape recorder is sufficiently light and compact to be employed in cases where extreme portability and completely automatic operation is required. Its principal disadvantage is that no immediate information can be obtained regarding concentration and dosage. The paper tape recorder is believed to be a satisfactory and useful instrument for obtaining information in respect to the concentrations of a given substance. The mechanical features of the present instrument appear to be satisfactory, although it would be profitable to undertake further instrumentation in respect to features of convenience. Its application to problems other than those considered is of course dependent upon the development of suitable impregnated paper tapes.

38.3.2 Sensitized Film Mustard Gas Recorder

In this instrument [16] an airstream containing mustard gas is saturated with water vapor and is impinged upon a sensitized gelatin film, advanced by clockwork, to give a trace of silver chloride, this can be developed and the optical density related to the mustard concentration of the sampled air through calibration of the instrument. The sensitive film is prepared by removing the silver halide emulsion

from standard positive 35-mm movie film and treating the latter with a solution of silver perchlorate. The instrument employed a centrifugal vacuum pump, operated by a small 6-volt motor, first, to draw air over methanol and through a combustion chamber and a heat-dissipating tube to maintain a constant temperature; second, to draw in the air to be sampled through a flow-regulating capillary and then through a water saturator, to impinge it through a jet upon a recording film, and then expel it; third, to draw clean mustard-free air through a regulated leak into the recorder container to maintain a noncontaminating and noncorroding atmosphere about the mechanisms and the film which is not in the immediate region being exposed to the sample. The film is advanced by a clock-driven mechanism at the rate of 3 inches per hour. After exposure the film is removed from the recorder, washed free of silver perchlorate, developed, washed, and dried. Photometric correlation of the net light absorption of the trace with known mustard gas concentrations permits a calibration curve to be constructed which can then be used to convert observed net light absorption along the trace to the mustard gas concentration existing in the air drawn into the recorder as a function of time. Thus, average concentrations over a 3- to 4-minute sampling period can be obtained from the curves relating concentration and time. The minimum concentration detectable by the instrument seems to be below 1 μg of mustard gas per liter. The film appears to be stable if kept dry and dark and reasonably cool and may be prepared weeks before use. One field test of the recorder showed values 5.5 per cent below the average total dosage bubbler value over a 4-hour period, and hourly values which deviate 7.5 per cent from bubbler values. Two other field trials showed fair correlation with the tape recorder and bubbler methods but the trials as a whole were not adequate tests. Because of its late development it was not possible to evaluate the instrument properly, although it does appear that in principle it is not so useful as the paper tape recorder (Section 38.3.1).

38.3.3 Pyrolytic Mustard Gas Recorder

An instrument was devised which depends upon the pyrolysis of mustard gas to form hydrochloric acid and the estimation of this latter substance colorimetrically.[1] This instrument does not require the use of electric power in that the mechanical parts are driven by clockwork and the injector-type air pump actuated by butane gas subsequently used as fuel for the pyrolyzing unit. The sample of the contaminated air is drawn by the injector through a quartz tube, a portion of which is heated by a gas burner. On passing over the heated portion of the tube, the mustard gas is pyrolyzed with the formation of hydrogen chloride. The airstream is then passed over a few drops of water contained in a depression in the tube, where the hydrogen chloride is partially absorbed. The sampling and absorption of the hydrogen chloride proceeds for a fixed period of time (9 minutes if the 15-minute cycle is used), after which the quartz tube automatically snaps into contact with the recording drum. The latter carries a chart of absorbent paper impregnated with Congo red and ruled with a water-repellent material into vertical strips about $\frac{1}{8}$ inch wide. The quartz tube impinges upon the drum in the center of one of these vertical strips, and as soon as contact is made with the paper, the water is drawn by capillary action through a small hole in the tube and drained out onto the strip. The strip of indicator is colored blue to a length which is dependent upon the amount of hydrogen chloride present; hence the length of blue measures the concentration of mustard gas in the incoming air sample. After remaining in contact with the paper for 4 or 5 minutes to allow time for the water to be completely drained, the tube begins to move away from the drum, and shortly thereafter a new charge of water is injected by a small pump. The entire process is then repeated on the next cycle, the recording drum in the meantime rotating to bring a new strip of paper into position for the next record. The instrument was designed to operate continuously without attention for 15 hours on a 15-minute cycle or for 30 hours on a 30-minute cycle. The record charts are about 16 inches long by $1\frac{1}{2}$ inches high and are divided into 60 individual record strips. When the end of a record chart is reached, the instrument's clock mechanism automatically stops itself.

The fuel tank holds $3\frac{1}{2}$ pounds of liquefied petroleum gas, which is sufficient to supply the burner for more than 30 hours. The butane enters the burner through an aspirating nozzle, simultaneously forming the flame that heats the quartz tube and furnishing the suction necessary to sample the air. The gas is delivered at constant pressure from a regulator, producing a constant sampling rate. This is adjusted by means of a rotameter flowmeter that is included in the suction line. Once adjusted, the instrument holds

an essentially constant flow rate of about 0.5 lpm for the duration of the sampling period. It is necessary to set the flow rate always to the same value since the mustard gas concentrations given by the calibration charts are valid only at the sampling rate at which the instrument is calibrated.

At the end of a period of sampling, the record sheet is removed from the drum and the records are read in the following manner: the ends of each blue strip are marked with a pencil and the length of blue is then measured in millimeters. It is now necessary to determine the length to which each strip was wet by water in which the hydrogen chloride was absorbed, since the length of blue produced by a given amount of hydrogen chloride is influenced by the extent of wetting of the strip. This is done by blowing hydrogen chloride vapor onto the record sheet from a bottle containing dilute hydrochloric acid. The acid vapor turns the paper blue everywhere except at the limits of wetting, which appear as pink lines against a blue background. Having measured the lengths of wetting in millimeters, the average mustard gas concentration during each 15-minute (or 30-minute) interval of the sampling period is found by reference to a calibration chart in which mustard gas concentrations are tabulated against millimeters of blue for various wetting lengths.

A calibration chart for each quartz tube is furnished by the manufacturer of the instruments. Each individual tube requires a separate calibration chart, since the efficiency of absorption of the hydrogen chloride is dependent upon the characteristics of the particular tube used. It is not necessary, however, that a quartz tube always be used in the same machine in which it was calibrated, since the flow rate at which different machines sample is set at the same value.

This recorder has several features which recommend it as a field sampling instrument: (1) it is a portable, compact unit and requires no batteries or external source of power, (2) its operation is automatic and it requires no attention from the operator during the sampling period, and (3) a time-delay starting device is included, by which the instrument can be set to start automatically at some predetermined time, from 0 55 minutes after setting; thus several instruments may be set by one operator to begin recording simultaneously.

The pyrolyzing recorder has several basic faults. The indicator action upon which it depends is not specific but will be given by any compound forming a hydrogen halide by pyrolysis. Volatile acids affect the indicator. This is a marked disadvantage in field assessment where acetic acid is being used in bubblers placed nearby. The quartz tubes are fragile. The absorption of hydrogen chloride is incomplete, causing sufficient corrosion within the instrument that it may fail to operate correctly. The device is usable only at concentrations of mustard gas up to 50 $\mu g/l$ and at concentrations above 2-3 $\mu g/l$. The blue boundary is indistinct so that large reading errors are inevitable. Temperature has a marked influence on the wetting of the paper. The apparatus frequently skips a record when water fails to drain from the quartz tube at the time of making contact with the record chart, probably because the capillary is dirty or air-bound. The instrument samples only for two-thirds of the time it operates. This may lead to a significant error in calculating total dosage.

38.4 MISCELLANEOUS INSTRUMENTS

In this section several instruments are described which were developed either as instrumental aids in the laboratory determination of mustard gas and other chemical warfare agents or as warning devices intended to alert exposed personnel to the presence of significant concentrations of certain chemical warfare agents.

38.4.1 Potentiometric Determination of Chloride Ion

Mustard gas, the nitrogen mustards, and a number of other chlorine-containing chemical warfare agents may be hydrolyzed or oxidized to chloride ion. This latter substance can then be determined by measuring the potential of a cell composed of a reference half cell and a silver silver chloride chloride ion half cell.[18] An alternative method is the conventional potentiometric titration with silver nitrate and suitable titrating and reference electrodes.[31]

38.4.2 Conductimetric Determination of Hydrochloric Acid

Air containing mustard gas is passed into a cell containing two electrodes and maintained at a temperature of 80 C. At this temperature the hydrolysis of mustard gas is reasonably rapid and the hydrochloric acid formed can be determined by measuring the conductivity of the solution. A recording milliammeter in a 110-volt circuit and in series with the

electrodes provides for a continuous record of the amount of hydrochloric acid formed and the amount of mustard gas introduced into the cell.[37]

38.1.3 Automatic Potentiometric Dosage Meters

An instrument was developed for the automatic detection of gases which react with silver ion to form an insoluble compound or complex ion.[7] In this instrument air containing the substance to be determined is passed through a silver-silver ion half cell and pure air passed through an identical silver-silver ion half cell. The complete cell is connected in series with a mirror galvanometer through appropriate series and shunt resistances. When the concentration of silver ion in the half cell through which the contaminated airstream was passed is decreased by reaction with the substance to be determined, the galvanometer deflects and a beam of light is reflected from the galvanometer mirror onto a photoelectric cell which in turn actuates a relay controlling a time indicator or some other signal. By altering the concentration of silver ion or the extent of galvanometer deflection needed to operate the photo relay, the instrument can be used to indicate the attainment of a given dosage. The limit of sensitivity appears to be about 2×10^{-7} mole chloride ion or 15 μg of mustard gas. A variation of the above instrument was also developed for the detection and determination of substances which react with bromine. In principle the operation of this latter instrument is similar to that of the automatic titrimeter described in Section 38.2.6. An airstream containing a low and controlled amount of bromine is passed through a cell containing a platinum electrode, dilute sulfuric and hydrochloric acids, and a 0.1 *M* silver nitrate silver reference electrode. The air to be sampled is introduced into the bromine-laden airstream prior to the latter's entry into the cell. In the absence of substances reacting with bromine, the potential of the cell is translated into a definite deflection of a mirror galvanometer. When an amount of substance equivalent to the bromine present is introduced, the potential becomes zero and the deflection of the galvanometer is altered. The galvanometer is arranged to operate a photoelectric relay so that when excess gas is present, the relay operates a signal. If the gas concentration drops below the equivalent bromine concentration, a potential difference is again established and the signal is turned off. The critical concentration required to operate the signal may be set at any desired mustard gas concentration provided that it is greater than about 0.2 μg of mustard gas per liter.

38.1.4 Automatic Photoelectric Dosage Meter

An apparatus was designed [8] to record the attainment of predetermined dosages of mustard gas and other chemical warfare agents by taking advantage of the change in light transmission of a cell containing a reagent which would react with the substance to be determined. Air containing the substance is passed through a cell containing a solution of Congo red, silver nitrate, or starch and potassium iodide, and superimposed between a light beam and a photoelectric relay. When the end point is reached the relay is actuated and in turn it operates a warning or timing device. The end point is a function of the concentration of the substance to be determined, the amount of reagent present, and the sensitivity of the photoelectric system.

Chapter 39

MISCELLANEOUS ANALYTICAL STUDIES

By Carl Niemann

39.1 INTRODUCTION

DURING THE COURSE of World War II, Section 9.3 of the National Defense Research Committee [NDRC], considered a number of problems other than those relating to the detection, identification, and field assessment of chemical warfare agents. These supplementary problems were concerned with (1) the determination of carbon monoxide, (2) the determination of the impregnite content of impregnated clothing, (3) the treatment of water contaminated with certain chemical warfare agents, (4) the determination of the vapor pressure of selected chemical warfare agents, (5) the determination of the structure of certain chemical warfare agents, and (6) the development of analytical methods for the determination of DDT. The last topic is discussed in Chapter 42 and will not be considered here.

39.2 DETERMINATION OF CARBON MONOXIDE

Division 9 sponsored two kinds of investigations on the determination of carbon monoxide: first, an evaluation of methods for the accurate determination of the carbon monoxide present in so-called standard samples prepared by the Bureau of Standards; second, the development of instrumental methods of analysis suitable for use under field conditions. The "standard samples" were necessary as standards in this second phase of the work.

39.2.1 Analysis of Carbon Monoxide–Air Mixture Standard Samples

The analytical methods used for determining the carbon monoxide content of the so-called standard samples were:

1. An acidimetric method in which carbon monoxide was oxidized to carbon dioxide over Hopcalite, the carbon dioxide absorbed in standard barium hydroxide solution, and the excess alkali titrated with standard acid.[14,22,59]

2. A gravimetric method in which carbon monoxide was oxidized to carbon dioxide over Hopcalite at 195°C and the carbon dioxide collected in a weighed tube charged with Ascarite.[14,38,59]

3. An iodometric method in which carbon monoxide was allowed to react with iodine pentoxide at 140–150°C, the iodine formed being collected in potassium iodide and titrated with standard thiosulfate solution.[14,59]

4. A second gravimetric method in which carbon monoxide was allowed to react at 175–200°C with mercuric oxide contained in a weighed tube and determining the loss in weight arising from the reaction, $CO\ (gas) + HgO\ (solid) \longrightarrow CO_2\ (gas) + Hg\ (gas)$.[28]

Numerous analyses were made using the methods described above and it was concluded that the mercuric oxide method was not only the simplest but the most reliable of those investigated for the analysis of carbon monoxide–air mixtures.

39.2.2 Instrumental Methods for Determining Carbon Monoxide in Air

Initially the objective was to develop a simple, portable instrument which could be used in the field to determine concentrations of carbon monoxide in the range of 0.01–0.1 per cent. It was intended that this apparatus be used as a test instrument to determine the amount of carbon monoxide arising from the firing of weapons in enclosed places such as ships, gun turrets, tanks, and fortifications. Interest gradually subsided in the original goal and shifted to the problem of determining carbon monoxide in airplane cabins where the chief source of the gas is engine exhaust. This change of objective imposed a different set of conditions in that it became important to be able to determine carbon monoxide in the presence of hydrocarbons. In addition it was necessary to determine markedly lower concentrations of carbon monoxide, and to be able to operate the instruments under greater variations of temperature and barometric pressure, these variations being sudden and occurring constantly rather than being seasonal and relatively slow. The characteristics desired were the following: (1) range of concentration determinable, for the Army 0–0.4 per cent, for the Navy 0–0.08 per cent; (2) limit of error, 0.002 per cent carbon

monoxide; (3) size and weight of instrument, 9 x 6 x 5 inches, 15 pounds or less; (4) time of response, reliable readings in 3 4 minutes or less; and (5) maximum power available, 300 watts for the Army, 30 watts for the Navy.

The instrumentation program sponsored by Division 9 was directed toward the exploitation of four reactions exhibited by carbon monoxide. These were (1) the exothermic oxidation of carbon monoxide over Hopcalite, (2) the reduction of mercuric oxide to mercury by carbon monoxide, (3) the reduction of complex palladium salts by carbon monoxide, and (4) the formation of carbon monoxyhemoglobin. The instruments developed were either of the thermometric or colorimetric type.

Thermometric Instruments

In the exothermic oxidation of carbon monoxide over Hopcalite, measurement of the heat of reaction provides a means of determining the concentration of carbon monoxide. This principle, previously employed in an instrument developed by the Mine Safety Appliance Company, was given further consideration. A simple thermometric apparatus was developed [1] in which air was passed, at the rate of 1.5 lpm, through a cell containing 1 g of Hopcalite. The heat of oxidation of carbon monoxide caused a rise in temperature which was measured by a specially designed mercury-in-glass thermometer placed immediately above the catalyst. The rise in temperature was found to be proportional to the concentration of carbon monoxide in the entering gases and the device was capable of measuring concentrations of carbon monoxide between 0.01 0.1 per cent in steps of 0.01 per cent. This simple device, which failed to meet operating requirements, was modified in an attempt to obtain a satisfactory instrument.

In the modified instrument,[2] air flowing at the rate of 1.5 lpm was passed through a 20-foot copper coil, through the catalyst and around the thermometer bulb. The above assembly was enclosed in an electrically heated thermostat which controlled the ambient temperature to within 0.1 C. The mercury-in-glass thermometer was equipped with platinum contacts placed at intervals along the stem. The thermostat was adjusted so that at thermal equilibrium the mercury thread just completed the circuit between the first and second contacts. The higher contacts were spaced to correspond to temperatures attained during the oxidations of selected concentrations of carbon monoxide. When the circuit was completed through the higher contacts, a light, meter, or relay was actuated. Unfortunately it was not found possible to place contacts closer to each other than about 0.5 degree, with the result that concentrations could be determined only in steps of about 0.01 per cent.

In view of the need of greater sensitivity it was decided to abandon the use of mercury-in-glass thermometers and to develop a device in which the temperature was measured by resistance thermometers.[2] This latter instrument consisted of four components: (1) the main instrument case, (2) an indicating meter, (3) the drier assembly, and (4) a suction gauge and regulating valve. The main instrument case contained the reaction cell and heat exchanger both in a common thermostated housing.

The cell design was of the parallel-flow type, in which the influent gas stream was divided into two parts. One part was passed through the catalyst charge where the heat of oxidation was effective in raising the temperature of a pair of resistance thermometers. The other part was passed through a charge of adsorptive but noncatalytic material (Columbia activated carbon) exposed to a second pair of identical resistance thermometers. Each of the four resistance thermometers constituted one arm of a Wheatstone bridge normally operated at constant applied voltage. The disposition of the oxidation and reference thermometers was such as to cause maximum bridge unbalance for a given temperature difference. Any difference of temperature between the two pairs of thermometers caused a current to flow through the microammeter connected across the bridge points. In the oxidation of carbon monoxide, this current is proportional to the concentration of carbon monoxide being oxidized. The use of the parallel-flow type of cell made it possible to eliminate substantially adsorption effects due to gasoline vapor, carbon dioxide, and similar gases and vapors, by producing equivalent heats of adsorption simultaneously in each cell chamber. The desiccant used was indicating Drierite.

The total weight of the four components including 3-foot lengths of MSA flexible hose was about 20 pounds of which 13½ pounds was in the main instrument case assembly. The main instrument case measured 9½ x 6¼ x 9 inches, and the indicating meter unit, 4½ x 4½ x 2¾ inches. In order to make combustion conditions independent of ambient temperature variations, the entire thermometric bridge was enclosed in a thermostated housing main-

tained at approximately 50 C and controlled by a Fenwal thermoswitch. The influent gas was passed through a suitable heat exchanger also controlled at this temperature.

This direct-indicating carbon monoxide instrument was tested at the Instrument Development Laboratory of the Naval Air Experimental Station, Philadelphia Navy Yard, to obtain information on the altitude and temperature characteristics. It was found that the instrument performed satisfactorily as indicated by zero and calibration checks made before and after the flights. This instrument was also checked against the standard cylinders of carbon monoxide air mixtures obtained from the Bureau of Standards and results could be read to ±0.001. Thus, it is clear that both the precision and accuracy of this instrument are high.

Colorimetric Instruments

A lightweight, compact, portable instrument, dependent upon the reduction of mercuric oxide at 175-200 C by carbon monoxide and subsequent estimation of the liberated mercury with a selenium sulfide test paper, was developed on a contract sponsored by Division 9.[34] In this instrument the sample was drawn into a cylinder by raising a plunger manually and then allowing the plunger to return to its initial position, thus forcing the sample through a reaction tube charged with a specially prepared mercuric oxide. The reaction tube was maintained at 175-200 C by means of a thermostated housing. The gases issuing from the mercuric oxide zone were passed through an unheated arm of the reaction tube and allowed to impinge upon a strip of selenium sulfide test paper contained therein. The presence of mercury caused a blackening of the test paper and the length of the stain was found to be proportional to the carbon monoxide content of the sample. Through the use of calibrated papers containing appropriate concentrations of selenium sulfide, measurement can be made over the range of from 0.0-3.0 per cent carbon monoxide with a relative accuracy over the entire range of 5-10 per cent. The time required for a determination was approximately 3 minutes. When carbon monoxide free air was passed through the apparatus, a blank equivalent to about 2 ppm of carbon monoxide resulted from the thermal dissociation of the mercuric oxide. The chief sources of error appeared to be the magnitude of the blank and the sharpness of the boundary of the stained area on the test paper. However, this sharpness increased with increasing selenium sulfide content of the test paper. The above instrument satisfied all operative requirements and was a truly portable instrument in that it was light, compact, simple, and easy to operate. When it was tested with standard carbon monoxide-air mixtures it was found that its precision was high and its accuracy was well within 10 per cent of the true values.

A photoelectric instrument based upon the reduction of either palladous silicomolybdate or palladous silicotungstate by carbon monoxide was developed.[35] In this instrument silica gel impregnated with one of the above palladous salts was transferred from a hopper into a cell placed between a light and a photoelectric cell. The meter was adjusted to zero, the sample passed at a predetermined rate and for a selected time through the cell, and the change in light intensity arising from the change in transmission through the cell observed on a calibrated milliammeter. The instrument was so constructed as to permit the ready elimination of the exhausted indicator from the test cell and the introduction of a fresh charge. Provision was also made for the convenient control of flow rate and sampling time. With palladous silicomolybdate gel, the range of the instrument was 0.001-0.5 per cent carbon monoxide and with palladous silicotungstate gel, 0.05-1.0 per cent carbon monoxide. Equipped with a silica gel trap in the sampling line the instrument appeared to be reasonably specific and the sensitivity met Service requirements. Although the above instrument appeared to satisfy Service requirements preference was given to other instruments.

The reaction of carbon monoxide with hemoglobin to form carbon monoxyhemoglobin was investigated with the intent of developing an instrument utilizing this reaction. Although considerable information was obtained relative to the spectrophotometric determination of hemoglobin derivatives and although a simple photoelectric colorimeter was developed, it was concluded [9] that the hemoglobin reagent was too unstable to permit its use and that other methods of analysis were superior.

The desire of the Armed Services to have at hand an instrument, usable under flight conditions, which would indicate the concentration of carbon monoxide present during relatively short time intervals appears to have been satisfied in the development of the Leeds and Northrup thermometric instrument [37] and the Beckman colorimetric instrument [36] already described.

39.2.3 Detection of Carbon Monoxide

In the course of investigations on the determination of carbon monoxide, considerable information was obtained relative to the detection of this gas. Although a number of different substances were studied,[12,13] none had the versatility of the palladous silicomolybdate indicator. It would appear that with the availability of the Bureau of Standards indicator using this reagent and the Farnborough (RAF) detector[53] which is a dipotassium palladium disulfite impregnated silica gel, it can be stated that the problem of the detection of carbon monoxide is well in hand provided adequate filters are included to remove hydrocarbon gases and other reducing materials. The carbon monoxide indicator provided in the Chemical Warfare Service M-9 detector kit is not adequate in this respect.

39.3 DETERMINATION OF IMPREGNITE CONTENT OF IMPREGNATED CLOTHING

The determination of "antivesicants" in impregnated clothing was an important routine determination in the development and surveillance of this type of garment. Aside from procedures suitable for laboratory use, methods were needed which could be used at depots, on shipboard, and in the field.

39.3.1 Laboratory Methods

Since all of the impregnites used in impregnated clothing were chloramides, a simple iodometric titration was adequate for their estimation. The impregnite was extracted with a suitable solvent, potassium iodide was added, and the liberated iodine titrated with thiosulfate.[50]

39.3.2 Field Methods

Field methods were of two general types. In one, that of the Army, no attempt was made to determine the actual impregnite content but the method was suitable for the indication of the presence or absence of a predetermined impregnite content. In the other, the Navy, the actual amount of impregnite present in a given area of cloth was determined.

Army Method. The method used by the Army was based upon the reaction of the chloramide with potassium iodide and the subsequent reaction of the liberated iodine with a predetermined amount of sodium thiosulfate. The presence of iodine, detected visually or with the aid of a paper impregnated with starch, served to indicate the presence or absence of a predetermined amount of impregnite.[4,45,47,51,52] A kit was developed which permitted these operations to be conducted under field conditions.[47,52]

Navy Method. A method was developed for determining the impregnite content of cloth which was based upon measurement of the heat liberated in the reaction between the chloramide impregnite and a mustard gas simulant such as phenylhydrazine.[3] It was found that an approximately linear relationship exists between the amount of heat developed and the impregnite content of the cloth.[3,46] This method was not considered suitable for field use by the Army [46] but, as it appeared to offer considerable promise for use on shipboard and in routine testing, its development through improved instrumentation was undertaken.[17] Two different types of instruments were designed [17] for use in the rapid evaluation of the protective capacity of impregnated clothing. These instruments were built for use with a specified amount of reagent on a definite area of clothing which was thermally shielded and separated by a fixed distance from a woven wire electrical resistance thermometer element. The temperature rise was measured by means of differential electrical resistance thermometers, the elements of which were cemented to the underside of gold caps. The thermometer unit was insulated from the thermometer housing by the short bakelite tube supporting the gold cap. The use of the two-element differential thermometer provided compensation for ambient temperature changes. The temperature rise was indicated by the deflection on the microammeter scale. In measuring the temperature rise in this particular instrument, the cloth is held rigidly by means of a plastic cap on the collar which surrounds the gold cap of the "hot" side. The cloth is thereby maintained at a fixed distance above the gold cap. This makes it possible to make many measurements without the trouble of cleaning the gold cap after each measurement. The limit of error of the direct-reading instrument was ± 0.1 g chloride ion $cm^3 \times 10^4$ and the limit of error of the simplified instrument was ± 0.25 g chloride ion $cm^3 \times 10^4$. The Navy found these instruments to be satisfactory for their intended purpose and purchased a number of the direct-reading type.

Other Methods. For purposes of record, attention is called to other methods suggested for determining the impregnite content of cloth.[4,39]

39.1 TREATMENT OF WATER CONTAMINATED WITH CERTAIN CHEMICAL WARFARE AGENTS

Considerable effort was expended in investigations relative to the treatment of water contaminated with certain chemical warfare agents in order that such water might be made potable. The investigations included a study of the chemistry of certain chemical warfare agents as water contaminants, the development of analytical methods suitable for control purposes, actual water treatment procedures, and a study of the effect of chemical warfare agents on aquatic life.[15,16]

39.1.1 Chemistry of Certain Chemical Warfare Agents as Water Contaminants

The development of rational treatment procedures was dependent upon having adequate information in respect to the hydrolytic and oxidative reactions exhibited by certain chemical warfare agents. This information was obtained for the more common chemical warfare agents.

Mustard Gas and Related Compounds.[a] The hydrolysis of mustard gas was studied and it was found that the nontoxic thiodiglycol (TG) and the toxic sulfonium salt from 2 moles of thiodiglycol and 1 of mustard (H·2TG) are formed in varying proportions depending upon the conditions employed. The conditions for the oxidation of mustard gas and its hydrolysis products were also investigated. The oxidizing agents employed included chlorine water, hypochlorites, ozone, hydrogen peroxide, and Halazone. All these agents readily and rapidly converted sulfides to sulfoxides. Further oxidation to the sulfone is rapid with chlorine and Halazone, but requires considerably longer time or more vigorous conditions with the other oxidizing agents. Chloramine-T reacted with mustard gas to form an insoluble, stable, moderately toxic, sulfilimine derivative; TG and H·2TG were oxidized to the sulfoxide by this reagent. The slightly toxic sulfoxide of mustard gas was extremely stable in water under all conditions. The slightly toxic but vesicant sulfone of mustard gas was unchanged after 17 days in distilled water at room temperature. In weakly alkaline solution, the sulfone rapidly lost hydrogen chloride to give divinyl sulfone. Divinyl sulfone was highly toxic intramuscularly and extremely lachrymatory, but in aqueous solutions at 100 ppm it was innocuous. Unpalatable but nontoxic thiodiglycol was readily oxidized to the nontoxic sulfoxide, which has practically no odor or flavor. Further oxidation gave the nontoxic sulfone which lost water readily on heating or slowly on boiling in water to yield nontoxic thioxane sulfone. The toxic sulfonium salt, H·2TG, was slowly hydrolyzed to thiodiglycol at room temperature, but rapidly in boiling water. The nonvesicant readily oxidizable polysulfides in Levinstein mustard make this material markedly more persistent than pure mustard gas in contact with water. An attempt to prepare a chlorinated disulfide led instead to excellent yields of β-chloroethylsulfinyl chloride, the postulated intermediate in the formation of mustard gas from ethylene and sulfur chloride.

Suspensions of *bis*(β-chloroethylthioethyl) ether (T) undergo hydrolysis at about half the rate of mustard gas to give a complex mixture of DB-3 positive sulfonium salts. No T glycol can be detected in the hydrolysate. The DB-3 positive sulfonium salt of T with 2 molecules of TG was prepared and studied. T sulfone as well as the two diastereoisomeric forms of T sulfoxide were also prepared and characterized. They are much less toxic than T. It was concluded that the DB-3 tests incorporated in the two Chemical Warfare Service water-testing kits will detect toxic concentrations of T sulfonium salts.

bis(β-Chloroethylthio)ethane (sesquimustard, Q) is extremely insoluble in water and its rate of dissolution is far less than that of either mustard gas or T. It would, therefore, constitute a much less serious problem as a water contaminant. From its rate of hydrolysis in aqueous dioxane, it is evidently about twice as reactive as T and about four times as reactive as mustard gas. Some factors related to the mechanism of hydrolysis of the mustards and related thiodiglycol sulfonium salts were studied. Q was converted by oxidation to the two diastereoisomeric disulfoxides and to the sulfone, and analogous products were prepared from Q glycol and from Q glycol dibenzoate. The oxidation products of Q and Q glycol were found to be relatively nontoxic.

Nitrogen Mustards.[b] A study was undertaken on the action of the three nitrogen mustards[18,19] as water contaminants. The nature of the hydrolytic transformation products was correlated with experimental observations on the changes in the toxicity, the ease of adsorption on activated carbon, the detection

[a] The reactions in water of the sulfur and nitrogen mustards[20,21,22,23,24,25] are reviewed in detail in Chapters 19 and 20.

[b] See Note a.

with DB-3 and the case of chlorination of these agents.

Arsenicals.[23,33] Arsenicals containing tripositive arsenic are hydrolyzed practically instantaneously on contact with water. Lewisite frequently forms hard lumps which consist of a polymeric modification of the oxide. Solutions of the arsenical agents are readily oxidized to the corresponding acids with a marked decrease in toxicity. Further oxidation is difficult. Lewisite may be readily removed by adsorption on activated carbon, but its arsenic acid is difficult to remove in this manner.

Cyanogen Chloride.[23,35] The hydrolysis of cyanogen chloride in water is a base-catalyzed reaction with a half-life time of 18 hours at *p*H 8 and of 180 hours at *p*H 7. Phosphate ion accelerates the rate of hydrolysis. In dilute solution, ammonia has little effect on cyanogen chloride, but sulfide ion reacts rapidly to form thiocyanate. Hypochlorite rapidly destroys cyanogen chloride and thus is a satisfactory decontaminant. The chlorine demand of cyanogen chloride is equivalent to that of the ammonia which would be formed by its hydrolysis. This agent is poorly removed by the best water treatment carbons, but the whetlerites are remarkably effective in its removal. This action appears to be a chemical degradation rather than an adsorption. Cyanogen chloride is considerably more toxic to fish than any of the other chemical warfare agents tested in this manner.

Fluorine Compounds.[23,34,35,36] Diisopropyl fluorophosphate is soluble in water to the extent of 1.5 per cent at 25 C. The primary hydrolysis to diisopropylphosphoric acid and hydrofluoric acid, at *p*H 3 8, has a half-life of nearly a week at 25 C. Neither the agent nor its primary hydrolysis products are affected by hypochlorite. Diisopropyl fluorophosphate solutions undergo a secondary reaction to yield acetone and isopropylphosphorous acid, but the factors governing this reaction have not been established.

Methyl fluoroacetate is soluble to the extent of about 15 per cent in cold water. It hydrolyzes slowly in distilled water. This hydrolysis is catalyzed more readily by alkali than by acid, so that in alkaline solution hydrolysis is rapid. Neither methyl fluoroacetate nor β-fluoroethanol is affected by dilute aqueous hypochlorite solution but use of vigorous oxidizing agents such as chromic and sulfuric acids results in complete cleavage to carbon dioxide, hydrogen fluoride, and water. Although the fluorine in methyl fluoroacetate is remarkably inert it does react with thiosulfate. One of the most interesting features of methyl fluoroacetate as a poison is its similar toxicity by mouth and by injection. This fact, coupled with the chemical difficulties of detection and decontamination, make it a very serious hazard as a water contaminant.

Water Denial Agents.[19b,35] Several of the compounds which were tested were found to show promise as water contaminants in concentrations of 1 ppm. The following six are arranged roughly in order of decreasing efficacy: quassin, skatol, methyl selenofluoroacetate, a mixture of quassin and skatol, mustard dimethylthioether, and thiovaleraldehyde. Incidental to the above observations it was noted that 1,3-butanedithiol had perhaps the most potent and disagreeable odor of any of the substances tested. Thus, although its susceptibility to oxidation precludes its use as a water contaminant, it might be worth consideration as an agent for producing a masking odor in very small concentration.

39.1.2 Analytical Procedures Suitable for Control Purposes in Treatment of Contaminated Water

Attention was given to the development of analytical procedures suitable for the quantitative estimation of (1) chlorine demand,[3,21,28,42,45,46a,35] (2) the mustards,[3,21,44,45,46b,c,d,46a,b] (3) the arsenicals,[3,9,19] (4) the fluorine-containing toxics,[46c,d,41,42] (5) hydrogen cyanide,[46c,d] and (6) cyanogen chloride.[29] In general these methods were based upon no new principles, but were adaptations, suitable for water analysis, of methods previously described. In order to provide for operation under field conditions, a kit was developed which included some of these methods. The tests for which apparatus and chemicals were provided were: (1) the DB-3 test for the mustards, (2) the molybdenum blue test for arsenic, (3) chlorine demand, (4) cyanide, (5) lead and thallium, (6) mercury, (7) selenium, (8) chlorides, (9) hardness, (10) alkalinity, (11) sulfate, (12) *p*H, and (13) residual chlorine. The last six tests were included at the suggestion of the Engineer Board to avoid having separate sets of equipment at the water supply points — one for chemical agents and one for general purposes.

39.1.3 Treatment of Contaminated Water

In general the procedures advocated[3,16,20,26] for the removal of the more common chemical warfare agents, or their hydrolysis or oxidation products,

from potable waters were modifications of standard water treatment practice in that both chlorination and treatment with activated carbon were used. Commercially available carbons were evaluated with respect to their efficiency in the removal of the common chemical warfare agents, or their hydrolytic or oxidation products, and considerable data were collected relating to the problem of establishing and maintaining suitable residual chlorine concentrations in contaminated water.[2,16,26,36]

39.5 DETERMINATION OF VAPOR PRESSURE OF CERTAIN CHEMICAL WARFARE AGENTS

In order to evaluate properly the potentialities of a number of recognized and candidate chemical warfare agents it was necessary to devote considerable attention to the accumulation of reliable vapor pressure data for a large number of compounds. It is not necessary to discuss these data here and it will suffice to call attention to the more important investigations in this field.[5–7,34,37a,b,c,38,37a,b,c,d]

39.6 DETERMINATION OF MOLECULAR STRUCTURE OF CERTAIN CHEMICAL WARFARE AGENTS

In mustard gas, the average of the carbon sulfur and carbon-chlorine bond distances is somewhat greater than would be expected from the values found in simpler molecules which contain these bonds. The chloroethyl sulfur groups in the mustard gas molecule have a planar, *trans* configuration. In the molecules of the methyl and ethyl amines, alcohols, ethers, mercaptans, sulfides, and chlorides, the bond distances and bond angles are all in close or identical agreement with the values found in earlier work. It is almost certain that dimethyl trisulfide has the straight chain structure. The nitrogen trifluoride molecule is pyramidal. The higher boiling isomer I of lewisite has the *trans* and the lower boiling isomer II has the *cis* structure.[27]

PART VI

MISCELLANEOUS INVESTIGATIONS

Chapter 40

SYNTHESIS OF COMPOUNDS FOR STUDIES OF LUBRICANTS AND HYDRAULIC FLUIDS

By *Jonathan W. Williams*

40.1 INTRODUCTION

THE WORK DESCRIBED in this chapter was undertaken with the broad objective of discovering superior components of hydraulic fluids and lubricating oils. The participation of Division 9 of the National Defense Research Committee [NDRC] in this program was limited to the preparation of compounds. All testing to determine the usefulness of the compounds was carried out by the Naval Research Laboratory.

The two main aspects of the program were (1) the preparation of a number of rare hydrocarbons, acids, alcohols, thiols, and esters for use in thin film studies, and (2) a study of methods suitable for the synthesis of fluorocarbons of interest as ingredients of noninflammable hydraulic fluids and lubricating oils.

In the first part of the program very pure samples of 52 hydrocarbons, 39 acids, 7 alcohols, 2 thiols, and 18 esters were prepared and turned over to the Naval Research Laboratory for testing. All of these substances were rare fine chemicals, the preparation of which would have taken several years had it been undertaken by a small group of chemists in a Service laboratory.

The work on fluorocarbons was in many aspects a pioneer search for practical routes to completely fluorine-substituted carbon-skeleton bodies. Two methods of considerable promise were devised. The simpler of these processes uses cobalt trifluoride as an agent for replacement of all hydrogen atoms in hydrocarbons by fluorine. Using this scheme a convenient pilot plant process has been worked out for the conversion of *n*-heptane to perfluoroheptane. The second process involves the polymerization of perfluorobutadiene. A good method of preparation of this monomer has been devised, and the polymerization to give a number of interesting products has been studied. Compounds prepared in the Division 9 program include 22 pure fluorocarbons and 17 miscellaneous fluorinated substances.

Tests conducted at the Naval Research Laboratory have demonstrated that fluorocarbons in general do not meet Navy specifications for hydraulic fluids and lubricating oils.[15] The compounds have short liquidus ranges and poor viscosity indices. The chemical stability, particularly the hydrolytic stability, was found to be poor.

40.2 MISCELLANEOUS COMPOUNDS FOR FILM STUDIES

At the request of the Naval Research Laboratory, NDRC undertook the preparation of many organic substances of interest in thin film studies devoted to determining the effect of additives in lubricating oils. The substances synthesized include several rare hydrocarbons, acids, alcohols, and esters. The syntheses are described in the individual reports[1–6] and the compounds made are listed in Tables 1–4. The use of many of these substances in the Navy testing program has been reported.[12–16]

40.3 FLUOROCARBONS

Publications in the open literature present claims to unusual stability for fluorocarbons.[17–28] The Naval Research Laboratory became interested in their possible use as noninflammable hydraulic fluids and lubricating oils. NDRC initiated a program of exploratory research aimed at devising suitable methods of synthesis. Compounds prepared as a result of these studies are listed in Tables 5–7.

It was agreed at the outset that six general methods of synthesis should be explored:

1. Reaction of elementary fluorine with carbon.
2. Replacement of hydrogen in hydrocarbons by fluorine.
3. Replacement of other halogens by fluorine.
4. Replacement of nitro or amino groups by fluorine (in the aromatic series).
5. Polymerization of small units.
6. Degradation of high molecular weight fluorocarbons.

REACTION OF FLUORINE WITH CARBON

Following leads in the literature,[17,18] a study was made[11] of the reaction of fluorine with carbon. This

TABLE 1. Compounds for thin film studies. Hydrocarbons.

Compound	Reference
Bicyclohexyl	3
1-Cyclohexyl-3-(4-dodecahydrodiphenyl)butane	4
1-Cyclohexyldodecane	1
2-Cyclohexyltridecane	4
Cyclopentene	2
Cyclopentylcyclopentane	2
1-α-Decalyl-2-cyclohexylethane	4
Diallyl	2
1,1-Dicyclohexyldodecane	4
1,1-Dicyclohexylethane	4
Dicyclopentylmethane	2
Diisobutyl	2
Diisobutylisoamylmethane	4
3,3-Dimethyl-1-butene	2
1,1-Dimethylcyclohexane	2
2,5-Dimethyl-7-cyclohexylheptane	4
2,6-Dimethyl-4-cyclohexylmethylheptane	4
1,1-Dimethylcyclopentane	2
1,2-Dimethylcyclopentane	2
1,3-Dimethylcyclopentane	2
1,2-Dimethylcyclopentene	2
1,3-Dimethylcyclopentene	2
2,6 Dimethyl-4-(α-decalylmethyl)heptane	4
2,11-Dimethyl-5,8-diisoamyldodecane	4
2,6-Dimethyloctadecane	4
2,4-Dimethyl-2-phenylhexadecane	4
Dineopentylethane	4
1,1-Diphenyldodecane	4
13-Docosen-4-ol	3
Dodecane	3
Dodecylcyclopentane	4
2-Ethyldecahydronaphthalene	3
2,4-Hexadiene	5
2-Hexene	2
Isoamyl-*p*-*t*-butylcyclohexane	4
1-Isoamyl-3-*t*-butylcyclopentane	4
1-Isoamyl-3,3,5-trimethylcyclohexane	4
1-Methylcyclopentene	2
2-Methyl-4-isobutylhexadecane	4
3-Methylundecane	5
2-Octene	2
2-Phenyltridecane	4
2,6,11,15-Tetramethylhexadecane	4
2,6,12,16-Tetramethyl-9-perhydrogeranylheptadecane	4
2,6,12,16-Tetramethyl-9-perhydrogeranyl-8-heptadecene	4
Tricyclohexylethane	4
1,3,5-Triethylbenzene	3
1,3,5-Triethylcyclohexane	3
2,6,11-Trimethyldodecane	4
2,6,11-Trimethyl-9-isobutyldodecane	4
Vinylcyclohexane	2
1-Vinyl-1-cyclohexene	2

TABLE 2. Compounds for thin film studies. Acids.

Compound	Reference
α-*n*-Amyldodecanoic acid	1
α-*n*-Amylnonoic acid	1
α-*n*-Amyltetradecanoic acid	1
n-Arachidic acid	1
α-*n*-Butyldecanoic acid	1
α-*n*-Butyldodecanoic acid	1
α-*n*-Butyltridecanoic acid	1
α-Cyclobutylmethyldodecanoic acid	1
α-Cyclobutylmethyltridecanoic acid	1
α-Cyclohexyltridecanoic acid	1
α-Cyclopentyldodecanoic acid	1
α-Cyclopentyltridecanoic acid	1
α-Cyclopropylmethylhexadecanoic acid	1
α-Cyclopropylmethyltetradecanoic acid	1
1-Dodecanesulfonic acid	1, 5
α-Ethylpentadecanoic acid	1
α-Ethyltridecanoic acid	1
α-*n*-Heptyldecanoic acid	1
α-*n*-Hexyldodecanoic acid	1
α-*n*-Hexyloctanoic acid	1
α-*n*-Hexylundecanoic acid	1
11-Hydroxyoctadecanoic acid	1
12-Hydroxyoctadecanoic acid	1
13-Hydroxyoctadecanoic acid	1
1-Isopropyl-2-methylcyclopentanecarboxylic acid	1
4-Ketostearic acid	1, 5
12-Ketostearic acid	1, 5
α-Methylhexadecanoic acid	1
α-Methyltetradecanoic acid	1
n-Nonadecanoic acid	1
$\Delta^{9,10;12,13}$-Octadecatrienoic acid	1
α-*n*-Octyldecanoic acid	1
8-Pentadecanesulfonic acid	1, 5
n-Pentadecanoic acid	1
α-*n*-Propyldodecanoic acid	1
α-*n*-Propylhexadecanoic acid	1
α-*n*-Propyltetradecanoic acid	1
Stearic acid	3
1,2,2-Trimethylcyclopentanecarboxylic acid	1

TABLE 3. Compounds for thin film studies. Alcohols, glycols, thiols, etc.

Compound	Reference
Ceratyl alcohol	3
Decamethylene glycol	1
1-Dodecanethiol	1
Elaidyl alcohol	3
2-*n*-Heptyl-1-nonanol	1
2-*n*-Heptyl-1-nonanol	3
Octadecamethylene glycol	1
Oleyl alcohol	3
8-Pentadecanethiol	1

was attempted by passing fluorine over sugar charcoal or Norit at elevated temperatures and by passing fluorine through a carbon arc. In neither case was there a significant yield of anything other than CF_4. There was, furthermore, a constant explosion hazard. This phase of the investigation was abandoned in view of these findings.

REPLACEMENT OF HYDROGEN BY FLUORINE

The direct reaction between elementary fluorine and various hydrocarbons was tried but abandoned because of the inevitably explosive nature of the reaction and the formation of tarry products.[1] Search for a fluorinating agent of intermediate power led

TABLE 4. COMPOUNDS FOR THIN-FILM STUDIES. ESTERS.

Compound	Reference
n-Amyl laurate	6
n-Amyl melissate	6
n-Amyl stearate	6
n-Decyl acetate	6
n-Decyl caprate	6
n-Decyl laurate	6
n-Decyl melissate	6
n-Decyl stearate	6
Melissyl acetate	6
Melissyl caprate	6
Melissyl laurate	6
Melissyl melissate	6
Melissyl stearate	6
Methyl melissate	6
n-Octadecyl caprate	6
n-Octadecyl laurate	6
n-Octadecyl melissate	6
n-Octadecyl stearate	6

eventually to the adoption of cobalt trifluoride as the agent of choice.[11] The reaction between a hydrocarbon and CoF_3 usually results in complete fluorination under the conditions described below. Typical reactions are:

$$C_7H_{16} + 32CoF_3 \longrightarrow C_7F_{16} + 32CoF_2 + 16HF$$

$$C_6H_4(CH_3)_2 + 20CoF_3 \longrightarrow C_6F_4(CF_3)_2 + 20CoF_2 + 10HF$$

The cobalt trifluoride may be conveniently regenerated:

$$2CoF_2 + F_2 \longrightarrow 2CoF_3$$

Best results have been obtained by a vapor phase reaction. The liquid hydrocarbon to be fluorinated is injected into a vaporizer maintained at a temperature about 100 C° higher than the boiling point of the liquid. The resulting vapor is then swept with nitrogen through a reaction tube containing cobalt trifluoride, in which a fresh surface is continuously exposed by means of slowly revolving paddles. The temperature of the reactor is graded from a starting point equal to that of the vaporizer, to about 400 C° at the exit end. The emerging products, hydrogen fluoride and the fluorocarbon, are collected in a trap and separated as immiscible liquids. The crude fluorocarbon constitutes the lower layer. It is drawn off, washed with mild caustic solution, and distilled.

In the cobalt trifluoride procedure, the hydrocarbon reactant studied most thoroughly has been *n*-heptane. The recovery of carbon compounds in the volatile liquid mixture produced is about 90 per cent. This crude reaction mixture has the following approximate composition:

Perfluoro-*n*-heptane	75%
High boiling material	15%
Perfluoromethylcyclopentane	6%
Perfluorodimethylcyclopentane	2%
Perfluoro-*n*-hexane	1%

Pure perfluoro-*n*-heptane is obtained by careful fractionation.

Replacement of Halogen by Fluorine

This exchange has been accomplished by means of a variety of fluorinating agents, all of which have been described in the open literature.[19,20] The principal agents used in the NDRC studies were fluorine,[7,8] hydrogen fluoride,[9,10] mercuric fluoride,[7,8] and antimony trifluoride pentafluoride.[7,8,10] Replacement of all chlorine atoms in chlorocarbons to obtain fluorocarbons was found impossible by any procedure tested. Thus when perchlorocyclopentene is treated exhaustively with SbF_5, the major product is perfluoro-1,2-dichloro-1-cyclopentene, and no completely fluorinated product is obtained.[8]

Experiments designed to produce fluorocarbons from hydrocarbons by alternate chlorinations and fluorinations proved to be too elaborate to be practical and were abandoned.[8] Octane is easily chlorinated to $C_8H_{18}Cl_2$, but replacement of these chlorine atoms by fluorine proved to be very difficult under the conditions tried. In view of the success attained in direct fluorination, these experiments were discontinued.

Replacement of Nitro or Amino Group by Fluorine

This type of replacement reaction has been found to provide the most convenient tool for the introduction of fluorine into an aromatic nucleus. The scheme used has been studied extensively by Schiemann,[21] and is commonly referred to by his name:

$$ArNO_2 + 6[H] \longrightarrow ArNH_2 + 2H_2O$$

$$ArNH_2 + HONO + HCl \longrightarrow ArN_2Cl + 2H_2O$$

$$ArN_2Cl + HF_4^- \longrightarrow ArN_2BF_4 + Cl^-$$

$$ArN_2BF_4 \xrightarrow{\text{heat}} ArF + N_2 + BF_3$$

The goal of one phase of the Division 9 program was the preparation of an aromatic fluorocarbon containing only carbon and fluorine and retaining the aromatic system of conjugated unsaturation.[9] This goal was not attained. Specifically, it was hoped to prepare perfluoromesitylene. In this study, fluorine atoms were attached to the open positions in the benzene ring (the 2, 4, and 6 positions) by successive Schiemann reactions. It was planned to replace all the side-chain hydrogen atoms by chlorine, and then substitute fluorine for the chlorine. It was found, how-

ever, that only six chlorine atoms (two per methyl group) could be introduced with ease. An attempt to replace these chlorine atoms by fluorine using HF was unsuccessful.

Polymerization of Small Units

Inasmuch as various fluoro-chloro-substituted ethylenes were commercially available, and since they provide simple hydrogen-free starting materials, studies were initiated on their polymerization. Because of the wealth of information available on the polymerization of butadiene and related dienes, the main emphasis in this part of the program was placed on a study of perfluorobutadiene.[10]

The diene is most conveniently synthesized by starting with trifluorochloroethylene. Pyrolysis at 550–560 C results in dimerization to give a mixture:

$$2CF_2{=}CFCl \longrightarrow CF_2Cl{-}CFCl{-}CF{=}CF_2$$

and

$$CF_2{=}CFCl{-}CFCl{-}CF_2$$

The open chain compound, $CF_2Cl\ CFCl\ CF = CF_2$, is the major component of the reaction mixture. When the unpurified mixture is chlorinated in sunlight, the cyclic component is unaffected while chlorine adds to the double bond of the olefin giving perfluoro-1,2,3,4-tetrachlorobutane. The reaction mixture then consists principally of perfluoro-1,2,3,4-tetrachlorobutane mixed with some perfluoro-1,2,-dichlorocyclobutane. The latter substance is removed by distillation and the residue is dechlorinated by refluxing with zinc in the presence of butyl carbitol.

$$CF_2Cl{-}CFCl\ CFCl\ CF_2Cl + 2Zn \longrightarrow CF_2{=}CF{-}CF{=}CF_2 + 2ZnCl_2$$

An alternate but somewhat less satisfactory route to perfluorobutadiene starts with *sym*-difluorodichloroethylene.[10] At −78 C fluorine reacts with this substance to produce a saturated dimer which is perfluoro-1,2,3,4-tetrachlorobutane:

$$2CFCl{=}CFCl + F_2 \longrightarrow CF_2Cl{-}CFCl{-}CFCl{-}CF_2Cl$$

Unfortunately the reaction is not clear-cut and the yield of desired product is rather low. Treatment with zinc may be carried out as described in the preceding paragraph.

The polymerization of perfluorobutadiene has been accomplished by three differing procedures. (1) Under the influence of *heat alone*, polymeric mixtures are formed, from which a dimer and a trimer have been isolated but not completely identified. (2) Similar results are obtained when perfluorobutadiene is subjected to the catalytic influence of *benzoyl peroxide*. (3) The effect of *fluorine* at low temperatures (approximately −78 C) is to induce dimerization with some fluorination. As the temperature is raised, the course of the reaction shifts toward saturation without polymerization.

Degradation of High Molecular Weight Fluorocarbons

Table 5. Fluorocarbons.

Compound	Reference
Perfluoro-1,3-butadiene	10
Perfluoro-*n*-butane	11
Perfluoro-1-butene	10
Perfluoro-2-butene	7
Perfluoro-cyclobutane	10
Perfluoro-cyclobutene	10
Perfluoro-2,3-dimethylbutane	10
Perfluoro-2,3-dimethyl-2-butene	10
Perfluoro-*m*-dimethylcyclohexane	11
Perfluoro-*o*-dimethylcyclohexane	11
Perfluoro-*p*-dimethylcyclohexane	11
Perfluorodimethylcyclopentane	11
Perfluoroethylcyclopentane	11
Perfluoro-*n*-heptane	11
Perfluoro-hexahydroindane	11
Perfluoromethylcyclohexane	11
Perfluoropropene	7
Perfluoro-1,3,5-trimethylcyclohexane	11
C_4F_{12}	10
$C_{12}F_{18}$	10
$C_{16}F_{24}$	10
$C_{20}F_{30}$	10

Table 6. Fluorochlorocarbons, fluorobromocarbons, and fluorochlorobromocarbons.

Compound	Reference
Perchloro-1,4-difluorobutane	10
Perfluoro-2-chloro-1,2-dibromopropane	10
Perfluoro-2,3-*bis*(2-chloroethyl)-1,4-dichlorobutane	10
Perfluoro-2-chloropropane	10
Perfluoro-2-chloropropene	8
Perfluoro-2,3-dibromobutane	10
Perfluoro-1,2-dibromopropane	10
Perfluoro-2,3-dichloro-1,3-butadiene	10
Perfluoro-1,4-dichlorobutane	10
Perfluoro-2,3-dichlorobutane	10
Perfluoro-1,1-dichloro-2-butene	10
Perfluoro-3,4-dichloro-1-butene	10
Perfluoro-1,2-dichlorocyclobutane	10
Perfluoro-1,2-dichloro-1-cyclopentene	8
Perfluoro-1,2-dichloro-3,4-dibromobutane	10
Perfluoro-1,2-dichloropropane	8
Perfluoro-3,3-dichloro-1-propene	10
Perfluoro-2,3-dimethyl-2,3-dichlorobutane	10
Perfluoro-1,2,3,4-tetrachlorobutane	10
Perfluoro-1,2,2-trichloropropane	8, 10
1,3,5-Trifluoro-2,4,6-trichlorobenzene	9
2,4,6-Trifluoro-1,3,5-*tris*(trichloromethyl)benzene	9
$C_4F_3Cl_5$	10
$C_4F_4Cl_4$	10
$C_4F_5Cl_3$	10
$C_4F_6Cl_2$	10

Although this item was on the original program, no work was done after receipt of a report from an industrial laboratory stating that the principal products of the thermal decomposition of polytetrafluoroethylene are perfluorocyclobutane and perfluorocyclopropane. These substances did not appear to be likely candidates for further synthetic work.

The fluorocarbons tested by the Naval Research Laboratory have not proved to be of interest as hydraulic fluid candidates.[14] *They were shown to have poor viscosity indices and short liquidus ranges, and to be chemically less stable than was anticipated.*

TABLE 7. Fluorohydrocarbons and fluorochlorohydrocarbons.

Compound	Reference
1,1-Difluoro-1-butene	8
2,4-Difluoro-6-iodomesitylene	9
2,4-Difluoromesitylene	9
1,1-Difluoro-1-propene	8
1,2,4,5-Tetrafluorobenzene	9
2,2,8,8-Tetrafluorononane	8
1,1,1-Trifluorobutane	8
2,4,6-Trifluoro-1,3,5-*tris*(dichloromethyl)benzene	9
2,4,6-Trifluoromesitylene	9
1,1,1-Trifluoropropane	8

40.4 FLUORINATED OXYGEN COMPOUNDS

As a side line to the study of fluorocarbons, information was obtained on the preparation and properties of several fluorinated oxygen compounds of interest. The compounds are listed in Table 8.

TABLE 8. Fluorinated oxygen compounds.

Compound	Reference
Difluoroacetic acid	8
2,4-Difluoro-6-acetylmesitylene	9
2,4-Difluoro-6-tribromoacetylmesitylene	9
2,4-Difluoro-6-trichloroacetylmesitylene	9
Ethyl γ,γ-difluoroacetoacetate	8
Ethyl γ,γ,γ-trifluoroacetoacetate	8
2,2,3,3,4,4-Hexafluoroglutaric acid	8
Trifluoroacetic acid	8
1,1,1-Trifluoroacetone	8
2-Trifluoroacetylmesitylene	9
1,1,1-Trifluoro-2,4-pentanedione	8

Trifluoroacetic Acid

A practical synthesis for this substance has been worked out using readily available materials.[7] The following steps are involved:

1. $CHCl_3 + CCl_2{=}CCl_2 \xrightarrow{AlCl_3} CHCl_2CCl_2CCl_3$
2. $CHCl_2CCl_2CCl_3 + NaOH \xrightarrow{C_2H_5OH} CCl_2{=}CClCCl_3 + NaCl + H_2O$
3. $CCl_2{=}CClCCl_3 + 8SbF_3 \longrightarrow CCl_2{=}CClCF_3 + 8SbCl_3$
4. $3CCl_2{=}CClCF_3 + 4KMnO_4 + 14KOH \longrightarrow 3CF_3COOK + 4MnO_2 + 9KCl + 3K_2CO_3 + 7H_2O$

Yields in the four steps are 95, 90, 85, and 85 per cent, respectively.

Difluoroacetic Acid

This substance may be prepared in a manner analogous to that used for trifluoroacetic acid.[7] The substance to be oxidized is $CHF_2CH{=}CCl_2$.

Hexafluoroglutaric Acid

This substance has been prepared by permanganate oxidation of perfluoro-1,2,-dichloro-1-cyclopentene.[7]

Ethyl γ,γ,γ-trifluoroacetoacetate

This ester has been produced by condensation of ethyl trifluoroacetate with ethyl acetate.[8] The product forms metal chelate compounds, such as the copper derivative, which are easy to prepare and hydrolytically rather stable, and which exhibit appreciable vapor tension.

Ethyl γ,γ-difluoroacetoacetate

This compound has been prepared by condensation of ethyl difluoroacetate with ethyl acetate.[8] Its properties and reactions are similar to those of the trifluoro compound.

1,1,1-Trifluoro-2,4-pentanedione

This fluorinated acetylacetone has been prepared by condensing ethyl trifluoroacetate with acetone.[8] Its copper chelate derivative has been found to be very stable and to have a higher vapor pressure than the corresponding nonfluorinated compound.

Chapter 41

SPECIAL FUELS FOR PROPULSION

By *Charles J. Mighton* and *Jonathan W. Williams*

41.1 INTRODUCTION

In its program on special fuels for propulsion, Division 9 was concerned with three different aspects of the general problem: (1) selection and testing of chemicals suitable for use as hydropulse fuels; (2) selection and testing of chemicals as candidate additives to improve the efficiency of gasoline in an aeropulse motor of the V-1 buzz-bomb type; and (3) a study of the process developed in Germany for the production of hydrogen peroxide from 2-ethylanthraquinone by successive hydrogenation and oxidation.

Among the compounds examined in the search for suitable hydropulse fuels, the performance of aluminum borohydride is most nearly in line with the specifications set up. This compound is far from ideal for the purpose as it is quite difficult to prepare, hazardous to handle, and unstable in storage, particularly under tropical conditions. Several other compounds are suggested for limited application and test usages. Among these are lithium hydride, lithium borohydride, and ethylaluminum sesquihydride.

Tests carried out in a V-1 aeropulse motor on adjuvants to increase the thrust obtained with gasoline failed to uncover any promising leads. The compounds studied included spontaneously inflammable materials and agents to lower or raise the octane or cetane rating of the gasoline.

A study of the preparation of hydrogen peroxide by successive hydrogenation and oxidation treatments of 2-ethylanthraquinone showed that quantitative yields of hydrogen peroxide are obtained and that the process may be repeated many times with no significant decrease in yield. By the use of a tetrahydro-2-ethylanthraquinone, it has been found possible to double the yield of hydrogen peroxide per cycle as compared to the 2-ethylanthraquinone process.

41.2 HYDROPULSE FUELS

The possibility of propulsion of devices such as torpedoes by means of the thrust obtained from an underwater gas jet was first given serious consideration in the British Admiralty Research Laboratory in 1938.[18] The idea received impetus in this country in 1943–1944 when Dr. F. Zwicky [19] suggested to personnel of the Naval Bureau of Aeronautics that underwater propulsion by the gas-jet scheme might be made practical if suitable chemicals could be provided which would react vigorously with water to generate a large volume of gas and a large amount of heat. Chemicals of this type might be utilized in devices designated as the hydroduct and hydropulse, in which the chemical compound is injected into a stream of water flowing through a duct. In the hydropulse fuel problem, chemicals have been selected for study largely on the basis of calculated specifications outlined by Dr. Zwicky.[19] The specifications indicated a need for complete reaction of the fuel with water at 25 C in 0.01 second or less and an evolution of at least 3,000 ml of gas, preferably hydrogen, per gram, and 5 Cal/g. Theoretical studies of the possibilities of the hydropulse have been made by two Office of Scientific Research and Development [OSRD] groups outside of Division 9.[9,10]

Among various compounds investigated as fuels for hydropulse devices, lithium hydride, aluminum borohydride, lithium borohydride, and ethylaluminum sesquihydride appear most suitable on the basis of laboratory tests. For a direct hydropulse, in which the fuel is injected into water, aluminum borohydride appears to be the best potential candidate since it is a liquid and reacts with water at 25 C in 0.006–0.015 second to liberate about 2,900 ml of hydrogen per gram (77 per cent of the theory). However, this compound is rather difficult to prepare and it presents problems in regard to instability on storage, particularly at elevated temperatures. A liquid product, believed to consist largely of ethylaluminum sesquihydride, has reacted with water in less than 0.01 second to liberate up to 754 ml of gas per gram. Although deficient in gas production, the latter candidate is obtainable from readily available materials and in view of its high rate of reaction would appear to merit consideration as a fuel for testing the hydropulse principle.

Lithium hydride and lithium borohydride, both of which are solids, react too slowly with water at 25 C to be of interest as fuels for a direct hydropulse, but they are believed to warrant testing in an "inverted"

hydropulse in which water is injected onto the chemical, with consequent higher reaction temperature and reaction rate. Possibilities of other water-reactive solids, such as sodium and calcium hydrides, lithium silicide, and certain beryllium compounds, have also been considered.

41.2.1 Lithium Hydride

In view of its availability and high theoretical specific gas production (2,820 ml/g), lithium hydride has received particular attention in the search for suitable hydropulse fuels.[2] The results of laboratory tests suggest that the chief problem in connection with the use of this candidate concerns development of suitable techniques for handling and injecting it as a very finely divided powder. Lithium hydride would appear to be an excellent candidate fuel for test in the "inverted" hydropulse where, instead of injecting the chemical into water, water is injected onto the chemical with consequent higher reaction temperature and reaction rate.

Commercial lithium hydride of about 97 per cent purity was found to liberate 3.7 Cal/g on reaction with water, and after micronizing to an average particle diameter of 4 μ reacted completely in 0.05 second to evolve 2,600 ml of hydrogen per gram. Material of 17 μ average particle diameter reacted in 0.10 second. Studies of lithium hydride powder containing various organic and inorganic compounds, including acids, anhydrides, oxidizing and reducing agents, and other metal hydrides, failed to uncover effective activators to increase the reaction rate.[2]

Attempts to develop satisfactory lithium hydride pellet and paste compositions which might be injected more easily than powders have been unsuccessful.[2] The smallest ($\frac{1}{8} \times \frac{1}{8}$ in.) pellets of 4- to 17-μ lithium hydride powders which were sufficiently compact for handling required from 2.5 seconds to react completely with water. Certain diluents, such as calcium hydride and citric acid in 25-50 per cent concentration, improved the rate of reaction, but in no case was the evolution of hydrogen complete in less than 1.5 seconds. To obtain free flowing pastes of lithium hydride powders, about 40-60 per cent of inert liquid diluents, such as amines, ketones, or others, was required, all of which greatly decreased the reaction rate. The best paste composition required at least 0.3 second for complete reaction with water; it gave only about 1,600 ml of hydrogen per gram and showed poor stability on storage.

41.2.2 Aluminum Borohydride

Aluminum borohydride is an outstanding fuel candidate on the basis of rate of reaction and specific gas production with water.[2,3,18] This material has an added advantage over many of the materials evaluated because it is a liquid, and would, therefore, probably be less difficult to inject. However, the compound is rather difficult to prepare and it presents problems which have yet to be solved in regard to instability on storage, particularly at elevated temperatures.

Liquid or vapor samples (0.02-0.1 g) of aluminum borohydride react with water at 25 C in 0.008-0.015 second to liberate about 2,900 ml of hydrogen per gram, or 77 per cent of the theoretical amount (3,760 ml/g). Analyses indicate that at least 99 per cent of the gas evolved is hydrogen. The heat of reaction has not yet been determined with certainty, but preliminary studies[3] have indicated $\Delta H = 2.3$ Cal/g. The heat of combustion has been shown to be approximately 13.8 Cal/g.[3]

Although the hydrogen evolution in the aluminum borohydride-water reaction is affected by temperature, as evidenced by an increase from about 72 per cent of the theory at 1 C to over 90 per cent at 95 C, the rate of reaction is not substantially changed.[3] Other investigations have shown that the *p*H of the water may determine the course of the reaction and, therefore, the specific gas production. Thus, with water at a *p*H of 1.9 (0.1 *M* phosphoric acid), substantially complete hydrogen evolution is obtained at 25 C, whereas under neutral or highly alkaline conditions the gas production was considerably less.

To assist in determining the utility of aluminum borohydride as a fuel for the more conventional self-contained jet motors, such as those employed for assisted take-off of planes, equivalent amounts of this candidate and water in the vapor phase have been reacted at elevated temperatures.[3] These tests, carried out with 0.01-0.03 g of aluminum borohydride at 85-110 C, showed that the gas evolution was nearly quantitative in reaction periods of 0.012-0.015 second. Although the results suggest that this fuel combination would probably be satisfactory, calculations made on the basis of preliminary heat of reaction data ($\Delta H = 2.3$ Cal/g) fail to indicate any marked superiority over nitromethane or gasoline and oxygen.

Aluminum borohydride was originally prepared by the reaction of diborane with trimethylaluminum [21]

$$Al_2(CH_3)_6 + 4B_2H_6 \longrightarrow 2Al(CH_3)_3 + 2Al(BH_4)_3$$

At the present time the most convenient process for preparation of this material consists of a metathetical reaction between sodium or lithium borohydride and aluminum chloride or bromide:[18]

$$3NaBH_4 + AlCl_3 \longrightarrow Al(BH_4)_3 + 3NaCl$$

Dry nitrogen is passed over a 7/1 mixture of aluminum chloride and sodium borohydride at 110–130 C. The relatively volatile aluminum borohydride is entrained and obtained in good purity in 80 per cent yield.

In attempts to synthesize aluminum borohydride by new routes, attention has been given to hydrogenation of triethylaluminum/triethylboron mixtures.[3] The only products obtained were unidentified, water-reactive solids formed at about 200 C. These solids, from which no aluminum borohydride could be isolated, are believed to have been produced as a result of the transitory formation and subsequent thermal decomposition of the desired product. With the exception of palladium-on-charcoal at 150 C or a ruthenium catalyst at 180 C, standard hydrogenation catalysts were inactive. No hydrogenation resulted at lower temperatures.

Attempts to prepare aluminum borohydride from methyl borate, aluminum chloride, and sodium hydride have also been unsuccessful.[3] No evidence has been obtained for the formation of aluminum borohydride in attempted hydrogenations of aluminum, aluminum amalgam, aluminum chloride, or lithium–aluminum alloy in the presence of triethylboron, or of aluminum halide sodium fluoborate mixtures with or without a halogen acid acceptor such as sodium hydride.

Stability studies with aluminum borohydride served to support the theory of transitory formation of this material in certain of the above hydrogenation experiments.[3] For example, when 0.050- to 0.010-g samples were pressured with hydrogen or nitrogen in a stainless steel bomb or in silver or chrome vanadium hydrogenation tubes at 150 C, substantially complete decomposition occurred in 2 hours. Solid decomposition products similar to those produced on hydrogenating triethylaluminum triethylboron mixtures were obtained.

41.2.3 Lithium Borohydride

Lithium borohydride is a white, hygroscopic solid which theoretically evolves 4,120 ml of hydrogen per gram on complete hydrolysis. Tests on this candidate showed it to react very slowly and incompletely with water at 25 C, and it appears, therefore, to be of little interest for use as a direct hydropulse fuel.[2,18]

Samples of high purity were found to require more than 10 seconds to generate about 5 per cent of the theoretical hydrogen with a large excess of water at ordinary temperatures.[2] Complete reaction, with a heat evolution of 3.3 Cal/g, was realized in dilute solutions only by maintaining a *p*H of 7 or lower. Among approximately 60 organic and inorganic materials tested as activators to promote faster and more complete reaction, only salts of palladium, cobalt, and nickel were found to be effective. However, even in 50 per cent concentration these materials failed to promote complete hydrogen evolution in less than 10 seconds at 25 C. Further tests demonstrated, on the other hand, that lithium borohydride reacts in about 0.05 second with an equivalent amount of water vapor at 107 C to evolve 3,500 ml of hydrogen per gram or 85 per cent of the theoretical amount. On this basis, it is believed that this candidate should merit further consideration as a fuel for use in "inverted" hydropulse or aeropulse-type jet motors which are designed to operate at high temperatures.

Lithium borohydride was first prepared by the reaction of ethyllithium with diborane.[22] The yield was low and the experimental technique was cumbersome. Several improved procedures have been worked out. Sodium borohydride, which is rather easily prepared from sodium hydride and trimethyl borate by reaction at 200 C,

$$4NaH + B(OCH_3)_3 \longrightarrow NaBH_4 + 3NaOCH_3$$

may be used in a metathetical reaction with lithium chloride in anhydrous isopropylamine,

$$NaBH_4 + LiCl \longrightarrow LiBH_4 + NaCl$$

to give a good yield of rather pure lithium borohydride. The desired product may also be obtained by the reaction of diborane with either lithium hydride[11,18] or lithium ethylate:[18]

$$2LiH + B_2H_6 \longrightarrow 2LiBH_4$$
$$3LiOC_2H_5 + 2B_2H_6 \longrightarrow 3LiBH_4 + B(OC_2H_5)_3$$

A new synthesis of lithium borohydride has been uncovered which involves the hydrogenation of lithium hydride triethylboron mixtures in cyclohexane.[1] In small scale experiments, lithium borohydride having a specific gas production of 3,900 ml g in dilute acid (corresponding to 94.7 per cent purity) has been isolated in about 58 per cent yield

from the crude reaction product by ether extraction. Further ether extractions yielded material of 97 98 per cent purity. The best results in a limited study of variables affecting this reaction have been obtained by conducting the hydrogenation at 240 C under a hydrogen pressure of about 3,000 psi. Preliminary experiments have indicated that the reaction is of general applicability and that the free metal may be employed in place of the alkali metal hydride. Thus sodium borohydride was obtained in good yield by hydrogenating triethylboron in the presence of sodium or sodium hydride. There is some evidence that calcium borohydride can be prepared by this method.

Attempts to prepare lithium borohydride by the reaction of alkyl borates with lithium hydride at elevated temperatures have indicated that some of the desired compound is obtained by this method, but the formation of large amounts of lithium alkoxides makes separation and purification of the product difficult.[1] In experiments carried out in refluxing Decalin (bp 190 C), lithium borohydride having a specific gas production of 2,155 ml/g was isolated. No lithium borohydride was obtained in attempts to hydrogenate alkyl borate/lithium hydride mixtures in cyclohexane at 240 C under a hydrogen pressure of 3,000 psi.

A careful study of the heat of combustion of lithium borohydride resulted in the acceptance of the value of 13,210 ± 30 cal/g.[8]

41.2.4 Alkylaluminum Hydrides

In the course of preparing triethylaluminum for test as a gasoline adjuvant, alkylaluminum *halides*, obtained readily from aluminum and alkyl halides, were found to react with lithium or sodium hydride to give extremely water-reactive alkylaluminum hydrides.[3-5] Studies have indicated that ethylaluminum sesquihydride, $C_2H_5AlH_2{:}(C_2H_5)_2AlH$, is the preferred candidate in this new class of compounds since it is a mobile liquid and reacts sufficiently fast with water. It will be noted, however, that none of the alkylaluminum hydrides meets the tentative specification requiring a gas evolution of 3,000 ml g. However, they should be of value for testing the hydropulse principle.

When ethylaluminum sesquibromide, $C_2H_5AlBr_2{:}(C_2H_5)_2AlBr$, was treated with lithium hydride in "isooctane" at 80 90 C, a spontaneously inflammable, mobile liquid was obtained in 71 per cent yield after removing the lithium bromide and evaporating the hydrocarbon solvent under vacuum.[3-5] Small samples of this liquid product, believed to be predominantly ethylaluminum sesquihydride but not completely identified as such, reacted with water at 25 C in about 0.005 second and liberated 754 ml of gas per gram, compared to 933 ml per gram theory for the pure compound. Analyses of the gas evolved in one case showed an ethane-hydrogen ratio of approximately 60/40. Reaction of ethylaluminum sesquichloride with lithium hydride in diethyl ether at 35 C gave substantially the same results although the liquid product obtained in this case was somewhat cloudy even after filtering. The reaction of ethylaluminum sesquichloride failed to proceed satisfactorily in ether when sodium hydride was used in place of lithium hydride.

Since methylaluminum hydrides would prove considerably more efficient as fuels because of higher specific gas productions with water, particular attention has been given to possibilities of methylaluminum dihydride and methylaluminum sesquihydride.[4,5] The products obtained on reacting the corresponding methylaluminum chlorides with lithium or sodium hydride have been found to vary considerably in their properties, however, depending on whether the preparation was carried out in hydrocarbons, such as *n*-hexane, or in ether. For example, reaction of methylaluminum dichloride (CH_3AlCl_2) with sodium hydride in *n*-hexane at 80 90 C has yielded viscous, spontaneously inflammable liquids which reacted with water in about 0.025 second to liberate up to 1,040 ml of gas per gram, compared to 1,520 ml theory for methylaluminum dihydride. Analyses of the gases evolved have shown a higher methane-hydrogen ratio than expected from the desired product (1.2/1 versus 1/2), indicating that more highly methylated derivatives are formed during some stage of the reaction, possibly through disproportionation. On the other hand, reaction of methylaluminum dichloride with lithium hydride in the presence of ether has given an ether-soluble, halogen-free, white solid as the principal product. The identity of this solid has not been established, but it is believed to be methylaluminum dihydride contaminated possibly with ether and complex materials of the type $LiAl(CH_3)_nH_{4-n}$. It is insoluble in *n*-hexane, contains some combined lithium, ignites spontaneously in air, and reacts vigorously with water to evolve 1,250 ml of gas per gram. Analyses of the gas evolved showed a hydrogen methane ratio of 1.6 1. Methylaluminum sesquichloride with sodium hydride in *n*-hexane at 90 100 C gave mobile liquids

which reacted with water in about 0.016 second to liberate up to 930 ml of gas per gram.[4] The reaction in ether at 35 C using lithium hydride in place of sodium hydride, gave a highly viscous liquid from which a gray-white solid deposited on standing. Although not positively identified, this solid appears to consist mainly of lithium aluminum hydride, $LiAlH_4$, a compound previously prepared by Schlesinger.[18] It was found to contain considerable combined lithium in addition to aluminum, hydrogen, and a small amount of carbon; on reaction with water it liberated 2,015 ml of gas per gram consisting of about 98 per cent hydrogen (2,358 ml/g theory for $LiAlH_4$). The liquid product, from which the solid was removed, gave only 660 ml of gas per gram and deposited additional water-reactive solids on standing at ordinary or elevated temperatures.

It appears from the above results that the reaction of methylaluminum dichloride and particularly of methylaluminum sesquichloride with lithium hydride results in a complexity of products, the individual components of which are difficult to isolate.[4] In any event, these studies have shown that liquid alkylaluminum hydrides can be obtained which react sufficiently fast with water to meet the tentative specification for a hydropulse fuel. The gas production (700–1,000 ml/g) of these novel candidates falls short of the value desired but it is believed that compounds of this type merit further investigation.

41.2.5 Beryllium Compounds

Preliminary tests of beryllium borohydride[18] indicate that this compound would be outstanding as a hydropulse fuel if practical methods of preparation and suitable techniques for injecting the solid into water could be developed.[4] In reaction rate studies, 0.07-g samples of beryllium borohydride appeared to react with water at 25 C in 0.010–0.015 second to liberate 4,000 ml of hydrogen per gram, or 87 per cent of the theory (4,630 ml/g).

Small samples of the mobile liquid, diethylberyllium, prepared from ethylmagnesium bromide and beryllium chloride, hydrolyzed completely in 0.020 second with excess water at 25 C to liberate 820 ml of the gas per gram, compared to 668 ml/g theory.[4] Analyses showed the gas evolved to consist of approximately 17–28 per cent hydrogen, 41–55 per cent ethane, and 23–27 per cent unsaturated hydrocarbon.

Attempts to prepare beryllium hydride by hydrogenation of diethylberyllium under 3,000 psi pressure have given a solid product believed to consist largely of ethylberyllium hydride.[4,5] This material reacted with dilute acid to liberate 1,340 ml of gas per gram, compared to 1,150 ml/g for ethylberyllium hydride.

41.2.6 Miscellaneous Compounds

Finely ground lithium silicide (Li_4Si_2), calcium hydride, and sodium hydride powders have been found inherently more reactive with water than lithium hydride but are considerably less efficient fuel candidates on the basis of hydrogen evolution. For example, calcium hydride of 6-μ particle diameter reacted completely with water in 0.03 second to evolve 970 ml of hydrogen per gram. Pellets (1/8 x 1/8 in.) of the powder required only 0.20 second compared to 2–5 seconds for similar lithium hydride pellets. Lithium silicide and sodium hydride reacted as powders in 0.01–0.03 second but as pellets in 2–4 seconds, respectively. These materials, though of less interest than lithium hydride as fuels for hydropulse devices, may have potential value where the quantity of chemical required to develop a high momentary thrust is not especially important.

Diborane with water or 0.1 *M* phosphoric acid evolved 4,200 ml and 4,600 ml of hydrogen per gram, representing 88 per cent and 96 per cent of the theoretical amount (4,850 ml/g) at 25 and 95 C, respectively, but the reaction required many seconds. In view of the slow rate of reaction and questionable stability of diborane on storage, this candidate has not appeared suitable as a hydropulse fuel. The synthesis of diborane has been studied by several groups. It may be prepared conveniently by the reaction of boron trifluoride etherate with such compounds as lithium hydride[19] or sodium borohydride.[19]

$$6LiH + 2BF_3\cdot(C_2H_5)_2O \longrightarrow B_2H_6 + 6LiF + 2(C_2H_5)_2O$$

$$3NaBH_4 + 4BF_3\cdot(C_2H_5)_2O \longrightarrow 2B_2H_6 + 3NaBF_4 + 4(C_2H_5)_2O$$

41.2.7 Test Methods

An important phase of the work on hydropulse fuels has been concerned with the development of laboratory methods for evaluating candidates on the basis of tentative specifications for gas evolution, heat evolution and rate of reaction with water. For rate studies, special reaction bombs were devised in which small samples of compounds in either solid, liquid, or vapor states could be tested; the time required for complete reaction with water was obtained from an oscilloscope record of the pressure surge picked up by

TABLE 1. Hydropulse Fuels.

Candidate	Physical state at 25 C°	Specific gas production (ml/g) in dist. H_2O at 25 C° Found	Theory	Reaction rate in seconds in dist. H_2O at 25 C°		Heat of hydrolysis at 25 C° (Cal/g)	Reference
B_2H_6	Gas	4,200	4,850	>30	(0.01 g)	..	1
$Be(BH_4)_2$	Solid	4,000	4,630	0.01–0.015	(0.07 g)	..	5
$LiBH_4$ (Note tests 2 and 3 under acidic conditions or at elevated temperature.)	Solid	(1) at pH = 7 200–400	4,120	>10	(0.025g)	3.3	1
		(2) at pH = 1.9 4,020	4,120	0.30	(0.040 g)	..	3
		(3) at 107 C 3,500	4,120	0.050	(0.020 g)	..	3
$Al(BH_4)_3$	Liquid	2,000	3,700	0.006	(0.015 g vapor)	2–3	1
		2,005	3,700	0.010–0.015	(0.030 g liquid-vapor)	..	3
		3,400 (95 C°)	3,700	0.012–0.016	(0.030 g vapor)	..	..
LiH (4-μ avg. particle size)	Solid	2,000	2,820	0.05	(0.07 g)	3.7	1
LiH pellets (4-μ) (3/8 x 3/8 in.)	Solid	....	....	2	(0.00 g)	..	1
$NaBH_4$	Solid	0	2,370	....	....	1.2	1
		2,200 (pH = 2)	2,370	very slow	....	..	..
$LiSi_2$ (0.7-μ avg. particle size)	Solid	1,300	1,000	0.06	(0.07 g)	4.4	1
CaH_2 (6-μ avg. particle size)	Solid	970	1,070	0.03	(0.07 g)	1.3 (calc)	1
NaH (20-μ avg. particle size)	Solid	810	930	0.01	(0.07 g)	1.1	1
$AlCH_3H_2$*	Liquid	1,040	1,520	0.016–0.025	(0.06 g)	..	4
$AlCH_3H_2$*	Solid	1,250	1,520	....			5
$Al_2(CH_3)_3H_3$*	Liquid	930	1,320	0.016–0.025	(0.07 g)	..	4
$Al_2(C_2H_5)_3H_3$*	Liquid	754	933	0.005	(0.1 g)	..	4
$Be(C_2H_5)_2$*	Liquid	820†	668	0.020	(0.07 g)	..	4, 5
Na-K Alloy (77/23)	Liquid	....	335	0.010 en 0.6–1.2	(50% completion) (100% completion)	..	1

* The identity and purity of these candidates has not been definitely established.
† The high gas production is due to the formation of ethylene and hydrogen during hydrolysis.

simple wire strain gauges of the Baldwin-Southwark type. A modified gas burette was employed for measuring specific gas productions, and an adiabatic Dewar calorimeter for heats of reaction.[1,3]

Data obtained in laboratory tests of the various hydropulse fuels discussed above and references to previous reports in which experimental details will be found are given in Table 1.

41.3 GASOLINE ADJUVANTS FOR AEROPULSE MOTORS

In efforts to improve the efficiency of gasoline as a fuel for aeropulse motors,[16] emphasis has been placed on testing gasoline containing small amounts of various agents for improvement of thrust and specific impulse. Spontaneously inflammable materials, and agents of known value in raising or lowering cetane or octane ratings of gasoline have received major attention.

The tests carried out failed to uncover any promising leads on adjuvants to increase the thrust or specific impulse obtained with 62 octane gasoline in a standard aeropulse motor of the V-1 buzz-bomb type.[5] The selection of compounds for study as additives was guided by the premise that more rapid combustion, possibly approaching constant volume burning, would be desirable, and that this might be obtained by the use of small amounts of (1) spontaneously inflammable materials or (2) agents to lower or raise the cetane or octane rating of the gasoline.

Spontaneously inflammable compounds in 2–13 per cent concentration with gasoline, such as butyllithium, triethylaluminum, triethylboron or mixed methylaluminum hydrides, gave either no improvement or inferior results.[5] In preliminary tests, 5 per cent of butyllithium with gasoline gave a specific impulse about 15 per cent higher than that of the control. However, further experiments with this fuel

combination in a motor with improved valves and a more accurate rotameter failed to confirm the advantage.

Cetane, when used alone as the fuel, in one test gave a 15 per cent increase over gasoline in specific impulse, but otherwise no correlation between octane and cetane numbers of different hydrocarbon fuels and their performance in jet motors was observed.[5] No advantage was gained by adding 5 25 per cent of typical diesel fuel accelerators or antiknock agents to gasoline, such as *s*-amyl nitrate, di-tertiary butyl peroxide, nitromethane, and tetraethyl lead.

41.4 PREPARATION OF HYDROGEN PEROXIDE

In view of the reported success attained in Germany with the preparation by a new route of hydrogen peroxide of high purity, work on the process [23] was initiated in this country. The method makes use of 2-ethylanthraquinone which is successively hydrogenated and oxidized, thus being used over and over again as a medium for the union of the elements making up hydrogen peroxide. In carrying out the procedure four different operations are involved: (1) reduction of the quinone, (2) removal of catalyst from the reaction mixture, (3) oxidation of the quinhydrone with air, and (4) removal of peroxide from the reaction mixture.

Laboratory studies have shown that the reduction of 2-ethylanthraquinone to the corresponding quinhydrone with subsequent oxidation gives quantitative yields of hydrogen peroxide.[6] The process may be repeated many times without a significant decrease in the yield of hydrogen peroxide.

A tetrahydro-2-ethylanthraquinone was prepared by quantitative reduction of 2-ethylanthraquinone, and was used in the above process.[6] It appears probable that, through the use of the tetrahydroquinone, the yield of hydrogen peroxide per cycle may almost be doubled over that obtained with 2-ethylanthraquinone. This is due to the fact that the tetrahydroquinone may be 90 per cent reduced to the hydroquinone with no precipitation of organic material from the reaction solvent, whereas no more than 50 per cent of 2-ethylanthraquinone can be reduced to the hydroquinone (i.e., to the quinhydrone stage) without precipitation.

Chapter 42

INSECT AND RODENT CONTROL STUDIES*

By Joseph Dee

42.1 INTRODUCTION

THE CONTROL of insects, other arthropods, and rodents were problems of major importance to the Armed Services during World War II, and a considerable amount of research on these problems was carried out before and during the war years. The investigations performed within Division 9 of the National Defense Research Committee [NDRC] were almost entirely of a chemical nature and represented a small portion of the total work done. Products developed in Division 9 were submitted to other laboratories for entomological evaluation and toxicity studies. This chapter is intended only to indicate the scope and results of the studies carried out within Division 9, although occasional mention of other work is made to clarify the presentation.

The investigations were concerned with DDT, insect repellents, miticide binders, and rodenticides. The chemical composition of the technical DDT produced in April, 1944, was determined. Formulations containing DDT were prepared for a variety of applications; especially noteworthy is a water-dispersible noncaking powder containing more than 90 per cent DDT. Several methods for the determination of DDT were developed and evaluated. About 2,100 candidate insect repellents were prepared; more repellency data are needed to evaluate adequately the better repellents uncovered during this study. Binders were found which extend the life of miticides impregnated in clothing. Efforts to find a rapid and accurate chemical method for the assay of the rodenticide, red squill, were not successful. Of the 98 compounds submitted for testing as rodenticides, sodium fluoroacetate (1080) has proved to be outstanding; about 1,000 pounds of 1080 were supplied for field tests by other organizations.

42.2 CHEMICAL COMPOSITION OF TECHNICAL DDT

Information regarding the chemical composition of technical DDT and the insecticidal potency and physiological action of its components was desired by the Armed Services for use in writing specifications. Samples of technical DDT obtained from three of the four companies producing DDT in April 1944, and a by-product oil obtained from the fourth company were studied.[1-3,26,36] Fourteen compounds were isolated from these samples and identified. 1-Trichloro-2,2-*bis*(*p*-chlorophenyl)-ethane (*p,p'*-DDT) comprised about 70 75 per cent of the technical product, and 1-trichloro-2-*o*-chlorophenyl-2-*p*-chlorophenylethane (*o,p'*-DDT) was present to the extent of about 20 per cent. Adequate amounts of the fourteen compounds were provided in a pure state, by isolation and synthesis, for entomological and physiological tests in other laboratories. The entomological data indicate that the insecticidal activity of technical DDT is due primarily to *p,p'*-DDT.[28] In larvicidal activity, *o,p'*-DDT is about one-fifth as effective as *p,p'*-DDT but is of little value against adult mosquitoes, houseflies, and body lice. 1,1-Dichloro-2,2-*bis*(*p*-chlorophenyl)-ethane (*p,p'*-DDD), which was present in small amounts, is as toxic as *p,p'*-DDT to mosquito larvae and adults but is less toxic than *p,p'*-DDT to houseflies and body lice.

Fractional crystallization, chromatographic separation, distillation in high vacuum, and cryoscopic analysis were employed to separate the components from each other. Results of the isolation studies are indicated in Table 1.

The presence in technical DDT of each of the fourteen compounds may be explained from a consideration of the possible reactions of technical chloral and technical chlorobenzene in the presence of sulfuric acid and subsequent reactions in washing the reaction product with an alkaline solution.

The recovery of identified compounds in the samples ranged from 80.6 93.5 per cent. The samples were not exhaustively studied. The oils which remained after all the solids that crystallized had been removed had elemental analyses similar to that of DDT isomers. These residual oils probably contained one or more DDT isomers in addition to the *o,p'*- and *p,p'*-isomers, although degradation of two of the oils did not lead to the formation and isolation of other than the *o,p'*- and *p,p'*-dichlorobenzophenones.

Seven of the fourteen compounds isolated from the

* Based on information available to Division 9 as of November 1, 1945, unless indicated otherwise.

TABLE 1. Composition of technical DDT.[38]

Compound	Sample 1[38] per cent	Sample 2[1] per cent	Sample 3[2] per cent	Sample 4[3] per cent
1-Trichloro-2,2-*bis*(*p*-chlorophenyl)-ethane (*p,p'*-DDT)*	(a) 66.7 (b) 72.0	(b) 70.5 (c) 63.5 (d) 64.5 (e) 67.9	(a) 72.7 (b) 70.7	...
1-Trichloro-2-*o*-chlorophenyl-2-*p*-chlorophenylethane (*o,p'*-DDT)‡‡	19.0	(c) 7.9 (d) 15.3 (e) 20.9	11.0†	71.8‡
1,1-Dichloro-2,2-*bis*(*p*-chlorophenyl)-ethane (*p,p'*-DDD)‡‡	0.3	4.0	0.17§	...
1,1-Dichloro-2-*o*-chlorophenyl-2-*p*-chlorophenylethane (*o,p'*-DDD)‡‡	...	...	0.044	...
2-Trichloro-1-*o*-chlorophenylethyl *p*-chlorobenzene sulfonate‡‡	0.4	1.85	0.57	0.11
2-Trichloro-1-*p*-chlorophenylethanol	0.2	...	...	...
bis(*p*-Chlorophenyl)-sulfone	0.6	0.1	0.034	...
o-Chloro-*o*-*p*-chlorophenylacetamide‡‡	...	0.01	0.008	...
o-Chloro-*o*-*o*-chlorophenylacetamide‡‡	...	0.007	...	...
Chlorobenzene	...	...	...	2.44
p-Dichlorobenzene	...	...	...	0.73
1,1,1,2-Tetrachloro-2-*p*-chlorophenylethane‡‡	...	...	...	+‖
Sodium *p*-chlorobenzene sulfonate	0.02	...	...	...
Ammonium *p*-chlorobenzene sulfonate	...	...	0.005	...
Inorganic	0.1¶	0.01**	0.01††	...
Unidentified and losses	6.5	5.1	10.6	19.4

* Letters in parentheses refer to analytical methods as follows: (a) Isolation from technical DDT, (b) recrystallization from 75 per cent aqueous ethanol previously saturated with *p,p'*-DDT,[37] (c) fractional crystallization, (d) adsorption analysis and fractional crystallization, (e) isolation, supplemented by cryoscopic analysis on the residue.

† This value does not represent all the *o,p'*-DDT present, as all only fractions were not exhaustively studied.

‡ Miscellaneous fractions containing *p,p'*-DDT, *o,p'*-DDT, and *p,p*-DDD.

§ Included is 0.08 per cent of *p,p'*-DDD isolated as such and 0.11 per cent of the corresponding olefin.

‖ Isolated as nitro derivative from an oil mixture analyzing for a mixture of $C_6H_4Cl_2$ and $C_6H_3Cl_3$ and representing 2.54 per cent of original material.

¶ Qualitative tests for ferric, lead, and magnesium carbonates were obtained.

** Insoluble in boiling 95 per cent ethanol.

†† Qualitative tests for ferric, ammonium, halide, and sulfate ions were obtained.

‡‡ Not described previously in the literature.

four samples examined had not been described previously in the literature. The structure of each of these compounds was established by elemental analyses and degradation to known materials, and confirmed by synthesis.

The identity of the compounds described previously in the literature was demonstrated by comparison with the reported physical properties, mixed melting point, and preparation of suitable derivatives.

During the course of this study a number of compounds were prepared that were either derivatives or intermediates of the compounds found in technical DDT. Limited efforts to synthesize the *o,o'*-isomer were unsuccessful.[1,34] The other compounds related to this study which were prepared include all six of the isomeric dichlorobenzophenones with one chlorine on each ring,[3] 1-chloro-2,2-*bis*(*p*-chlorophenyl) ethane (DDM),[1] 1-trichloro-2-*m*-chlorophenyl-2-*p*-chlorophenylethane (*m,p'*-DDT),[2] and the olefins formed by dehydrohalogenation of the several isomers of DDT.[1,3,28]

12.3 DETERMINATION OF DDT

Methods studied within Division 9 for the analysis of DDT were based on infrared and ultraviolet absorption spectroscopy, cryoscopy, estimation of the phosgene liberated upon oxidation of DDT with chromic acid, Beilstein test for halogen, and color formation by treatment of nitrated DDT with alcoholic alkali. Publications in the open literature on methods for the analysis of DDT have been summarized elsewhere.[39]

Infrared Spectroscopy

Infrared spectroscopy was successfully applied to the characterization of technical DDT, determination of the relative proportions in which a compound occurs in different lots of technical DDT, and the quantitative analysis of DDT in unknown solutions.[14]

A study of the infrared absorption spectra of samples of DDT and *p,p'*-DDT, *o,p'*-DDT, *m,p'*-DDT, *p,p'*-DDD, *bis*(*p*-chlorophenyl)-sulfone, 1,1-dichloro-2,2-*bis*(*p*-chlorophenyl)-ethylene, and 2,2,2-trichloro-1-*o*-chlorophenylethyl *p*-chlorobenzenesul-

fonate resulted in the assignment of absorption bands to structural units characteristic of these compounds. Comparison of the infrared spectrum of a sample of technical DDT with the assigned absorption bands thus permits qualitative determination of most of the compounds comprising the sample. The relative proportions in which a compound occurs in different samples of commercially produced DDT can be determined by a comparison of the absorption coefficients (expressed as $\log_{10} I_0/I$, where I_0 is the transmitted radiation at zero concentration and I is the transmitted radiation of the sample) of the different samples at the appropriate characteristic wavelengths. The quantitative analysis of DDT in unknown solutions is accomplished by comparing the per cent of transmission of the unknown sample at a characteristic wavelength with a reference curve obtained by plotting known concentrations against per cent of transmission.

The infrared absorption spectrum of a sample of DDT can be obtained from as little as a 1-mg sample. About 45 minutes is required to record the complete spectrum over the range from 1–15 μ. If only the range from 7–12 μ is examined, a record can be made in about 10 minutes. The quantitative analytical procedure for determining the concentration of DDT can be completed in less than 30 minutes, preserves the sample, and permits analysis of samples too small for gravimetric or volumetric methods. The experimental error of the method with dilute solutions (0.25 per cent) is about 10 per cent and with more concentrated solutions (1–25 per cent) is about 3 per cent.

Ultraviolet Spectroscopy

Studies of the ultraviolet absorption spectra of technical DDT and several of its components indicated that ultraviolet spectroscopy could not serve as the basis for a useful procedure for the analysis of technical DDT.[14] A detailed study of the curves over the whole wavelength range seems necessary to reach even a tentative conclusion. Ultraviolet absorption data were obtained for *p,p'*-DDT,[14] *o,p'*-DDT,[14] *m,p'*-DDT,[6] *p,p'*-DDD,[1] 2-trichloro-1-*o*-chlorophenylethyl *p*-chlorobenzenesulfonate,[6] four samples of technical DDT,[4] a by-product oil,[3] tetranitro-*p,p'*-DDT,[6] tetranitro-*o,p'*-DDT,[6] and the *o,o'*-, *o,p'*-, and *p,p'*-dichlorobenzophenones.[6]

Cryoscopic Analysis

A general method for determining the composition of a mixture depends upon determination of the freezing point depression produced by that mixture (1) in a solvent not a component of the mixture, and (2) in the solvents known or suspected to be components of the mixture.[41] In principle this method may be applied for each component of the mixture, but in practice it is employed only for components present in substantial amounts. Using this procedure the *o,p'*-DDT and *p,p'*-DDT contents of two residues obtained during a fractionation of a sample of technical DDT were determined.[4]

Estimation of DDT by Phosgene Method

The method for the determination of DDT which is based upon the oxidation of DDT with chromic acid and estimation of the liberated phosgene[28] was studied and its sensitivity improved.[8] An apparatus suitable for the determination was designed. The phosgene is swept through a small area of sensitized paper by a slow stream of air, and the intensity of the colored spot is related to the amount of DDT in the sample with the aid of a calibrated reference curve. Under conditions of maximum sensitivity the method is suitable for samples less than 1 μg. The experimental error may be 10–15 per cent. Technical DDT, *p,p'*-DDT, and *o,p'*-DDT yield results identical within limits of experimental error.

Detection of DDT on Lacquered Surfaces

A method based on the Beilstein test for halogen was developed for the detection of DDT on lacquered surfaces.[25] The method involves wiping the lacquered surface with a cellulose absorption mat impregnated with copper carbonate. This mat is then burned in a special burner which eliminates the yellow color in the flame and makes possible the detection of the green color against a dark background. The quantity of DDT can be estimated roughly from the intensity of the green color. The test is sensitive to 10 μg of DDT, can be carried out in less than 1 minute, and is not affected by sodium chloride. It would be possible to make a kit good for 1,000 or more tests, weighing less than 1 pound, and occupying a volume of about 10 cubic inches. This method was not studied exhaustively.

Color Test for *p,p'*-DDT

The method for the determination of *p,p'*-DDT which is based on the production of a blue color when tetranitro-*p,p'*-DDT is treated with methanolic sodium hydroxide[38] was investigated with the objective of increasing its sensitivity (10-μg sample required) and shortening the time necessary to carry

out the test (3–4 hours, although several samples can be run concurrently).[8a,b,c] Limited studies indicated a modified procedure which involves nitration of the sample followed by treatment with methanolic potassium hydroxide to be satisfactory for the quantitative determination of *p,p'*-DDT in the absence of appreciable amounts of the by-products normally present in technical DDT. A simple colorimeter suitable for use in the field was devised. The procedure appears to be sensitive with samples as small as 3 μg, can be completed within 15 minutes, and is accurate to about 20 per cent.

42.4 DDT FORMULATIONS

Dispersible DDT Powders

The Armed Services wanted DDT formulations with a high DDT content in order to save transportation space. Concentrates which were self-emulsifiable in water and contained 20–25 per cent technical DDT were used extensively. Studies directed toward the development of water-dispersible powders to contain at least 90 per cent DDT were successful.[11] The dispersible powders developed during this study generally contain an anticaking agent and dispersing agents in addition to the DDT, and can most simply be prepared by passing the blended components through a micronizer. They do not cake during prolonged storage at 65 C and require only manual mixing with water to produce well-dispersed suspensions which are equal in insecticidal effectiveness to emulsion concentrates or oil solutions of DDT.

Tests against insects showed that the effectiveness of suspensions of DDT increased with decreasing particle size over the range from 22 μ to about 0.5 μ. Methods involving micronization, wet ball-milling, and emulsification of molten DDT in water were found satisfactory for the comminution of DDT, with micronization proving to be the most practical. Micropulverizing, colloid milling, and viscous mixing were unsatisfactory. Aerosol grade DDT or technical DDT purified by crystallization or solvent extraction could be readily micronized, whereas technical DDT tended to pack in the micronizer.

The resistance of DDT to caking at high temperatures was increased by (1) using DDT consisting essentially of *p,p'*-DDT, (2) isolating the DDT particles from one another by means of a finely divided, low-density solid diluent or anticaking agent, and (3) coating the DDT particles with a film-forming material. Purified DDT is resistant to caking at 55 C but not at 65 C; the use of either anticaking agents or film-forming materials with purified DDT yielded products which did not cake in storage at 65 C for several months. Silica aerogel and carbon black were the most effective anticaking agents which were found, although low-density silicic acid, calcium silicate, expanded vermiculite, micropulverized asbestos, hydrated alumina, and a diatomaceous earth also were effective. Low bulk density seems to be a prime requirement for an anticaking agent. Non-caking DDT powders were produced by coating the individual particles with protective films of water-soluble polymeric materials such as methyl cellulose and polyvinyl alcohol; however, since these coated products are prepared by a rather lengthy process, more attention was devoted to the development of the much simpler micronizing process.

A considerable number of dispersing agents were examined; of them Igepon T [$C_{17}H_{33}CON(CH_3)C_2H_4SO_3Na$] and polyvinyl alcohol (grade RH-623) are outstanding. These agents performed well with different lots of purified DDT, are compatible with various types of anticaking agents, and give products dispersible in hard water. In some formulations more than one surface-active agent were used; the auxiliary agents seem to increase the wettability of the powders and supplement the dispersing action of the principal agent.

Several attractive dispersible DDT powders were prepared during the course of these studies. The percentage compositions of three of the preferred powders are given in Table 2.

Table 2. Percentage composition of three representative dispersible DDT powders.

Components	Powders 1	2	3
Aerosol grade DDT	90.5	90	90
Silica aerogel (Santocel)	6	7	6
$C_{17}H_{33}CON(CH_3)C_2H_4SO_3Na$ (Igepon T)		3	
Dibutyl phenylphenol disulfonate (Aresklene 400)	0.5		3
Polyvinyl alcohol (grade RH 623)	2		
Naphthalene formaldehyde sulfonate (Daxad 11)	1		1

Samples of powders of the types indicated in Table 2 have been supplied to the U. S. Army, Navy, Department of Agriculture, and other organizations for further practical evaluation. The laboratory development of these powders is substantially completed. Since space for transportation presumably will be less valuable in time of peace than during the

recent war years, these dispersible powders of high DDT content will be compared critically with formulations of lower DDT content to determine whether production of a high DDT content product is desirable.

Dispersible DDT Pastes

Need by the Armed Services for practical formulations with a high DDT content prompted studies on concentrated aqueous pastes of finely divided DDT in addition to work on emulsion concentrates and dispersible powders.

Water-dispersible pastes containing 50–70 per cent technical DDT have been developed.[12,32] These pastes are resistant to settling or agglomeration during storage at 55 C and are readily dispersed to give dilute suspensions for spraying. A typical composition is ball-milled DDT (53 per cent), sodium lignin sulfonate (1 per cent) as dispersing agent, polyvinyl alcohol (1.2 per cent) as stabilizing agent, and water (44.8 per cent). The two prime requirements for a paste to be stable at 55 C were shown to be (1) complete deflocculation of the DDT particles and (2) stabilization by means of a protective colloid to prevent either settling or aggregation of the particles during storage.

The studies on aqueous pastes which have been carried out are not exhaustive but can serve as a good background for any additional work on DDT pastes. Use of purified DDT should give pastes stable at temperatures above 55 C, and the maximum concentration of DDT in pastes remains to be determined. While pastes avoid the use of the flammable solvents present in emulsion concentrates, dispersible powders containing at least 90 per cent DDT, which contain neither solvents nor water as diluents, are inherently more attractive.

Solvents for DDT

A variety of solvents and solvent systems for DDT were evaluated with the objective of finding solvents or solvent combinations for application in emulsion concentrates, concentrated solution sprays, and solutions containing a high percentage of DDT which would be suitable for dilution with oils available in the field.[10] Several attractive solvent systems were uncovered.

A system comprising 80 parts of Solvesso No. 3 (a hydrogenated naphtha) and 20 parts of cyclohexanone dissolves 75 parts of DDT and has a flash point of 135 F. It seems satisfactory with respect to flash point, noncorrosiveness to plastics, low toxicity, and water emulsifiability. Solvesso No. 1 (flash point < 100 F) is equal to xylene in solvent power, and in combination with 10 per cent of cyclohexanone or methyl ethyl ketone the solvent action is equal to that of cyclohexanone, which dissolves an equal weight of DDT to give a 50 per cent solution. Methyl ethyl ketone, isophorone, and mesityl oxide are among the polar solvents found to be equal to cyclohexanone in solution capacity for DDT. A number of hydrocarbon solvents were examined.

Propylene oxide and ethylene oxide were found to possess outstanding solution capacity for DDT (170 g and 130 g DDT/100 g solvent, respectively). These solvents are too volatile for use in emulsion concentrates but merit investigation as auxiliary solvents for aerosol systems. In a scouting experiment a standard Army issue aerosol bomb was charged with 10 per cent DDT (threefold increase over the standard system), 7.5 per cent ethylene oxide, and 82.5 per cent Freon and was found to spray satisfactorily as a fine aerosol. Toxicity and explosion hazards of systems containing these alkylene oxides were not explored.

Surface-Active Agents for Emulsifiable DDT Concentrates

The development of DDT concentrates self-emulsifiable in water was desired by the Armed Services in order to save shipping space. The first DDT emulsion concentrate recommended to the Armed Services was comprised of 20 per cent DDT, 60 per cent xylene, and 20 per cent Triton N-100 (a polyethylene glycol octylphenyl ether).[28] Alternate formulations were desired to help insure adequate supplies and if possible to lower costs without decrease in quality. A survey of 90 surface-active agents for use in DDT emulsion concentrates was made.[12]

In laboratory tests Ammonyx 00 (oleyl dimethylamine oxide), Alkanol WXN (sodium hydrocarbon sulfonate), Ninol 737 (C_{16}–C_{18} acid-alkylolamine condensate), Phi-O-Sol (sodium ricinoleic sulfonate), and MP-646 (sodium hydrocarbon sulfonate) were found to be at least as effective as Triton N-100 in emulsion concentrates containing xylene or Solvesso No. 1. It was found that a concentrate containing 11 per cent DDT (the high DDT content is noteworthy), 6 per cent Ammonyx 00, 15 per cent Solvesso No. 1, and 5 per cent cyclohexanone readily gave an aqueous emulsion of excellent stability.

During the course of this survey the availability

of Triton N-100 improved, its cost decreased sharply, and a concentrate containing 7 instead of 20 per cent Triton N-100 was found to be satisfactory [29] so that the need for alternate surface-active agents became less critical.

Spreading Agents for Larvicidal Oils on Water

Unmodified oil solutions of DDT do not spread readily over water covered by a biological film, a thin surface film produced by organisms or arising from their decomposition. A survey was made of surface-active agents which might promote the spreading of oil solutions of DDT over water and render the oil film more resistant to compression by wind and water currents.[9] Laboratory data indicated Pentamul 87 and Pentamul 126 (esters of pentaerythritol) and SP-315 (alkali metal petroleum sulfonate) to be the most promising of the 48 surface-active agents examined during this study. Field tests showed that Pentamul 126, SP-315, and Triton N-100 were equally effective in increasing the spreading of oils over water not covered with a biological film. Over water covered with a biological film Triton N-100 was superior to Pentamul 126 and SP-315.

Emulsifiable Concentrates for Fly and Odor Control

The problem of controlling fly larvae and odor around latrines and corpses was important to the Armed Services in the Pacific areas. Formulations containing DDT for the control of adult flies, crude dichlorobenzenes for the control of eggs and maggots, and creosote for masking odor were developed.[16] Samples of six concentrates self-emulsifiable in sea water were submitted to the Chemical Warfare Service for field evaluation.

42.5 INSECT REPELLENTS

Mosquito-borne diseases have been a major problem to our Armed Services, especially in areas outside of the United States. The routine use of atabrine and the control of mosquitoes with DDT and sanitation proved to be invaluable during World War II. In newly occupied and combat areas, repellents applied to skin and clothing were particularly useful in giving protection from vectors of malaria and other diseases.

At the request of the Armed Services, a search for new and effective insect repellents was undertaken in 1942 by the U. S. Department of Agriculture, Agricultural Research Administration, Bureau of Entomology and Plant Quarantine, with funds made available by the Office of Scientific Research and Development. Candidate insect repellents obtained from industrial sources and Department of Agriculture laboratories were tested in Orlando, Florida, against caged *Aedes aegypti* and *Anopheles quadrimaculatus*. The more promising materials were tested in the field against other mosquitoes and flies. As a result of these studies a mixture, known as 6-2-2, consisting of 6 parts of dimethyl phthalate, 2 parts of 2-ethylhexanediol-1,3 (R-612), and 2 parts of indalone, and also the individual components were standardized by the Armed Services in 1943.[29] While 6-2-2 was markedly superior to insect-repellent compositions previously available, its protection time of 1–5 hours, depending upon conditions, was not considered adequate. The Army wanted an insect repellent effective for at least 12 hours.

In June 1944, NDRC Division 9 was requested to cooperate in the research program to find a longer lasting insect repellent by supplying samples of candidate insect repellents for tests in Orlando. It was felt that a carefully organized synthetic approach based on leads indicated by the repellency data might yield satisfactory repellents more rapidly than the method of simply testing any compound that might become available.

Repellents Tested on Skin

Compounds which were liquid at room temperature (testing of solids is described in Section 42.5.2) were screened by a method involving application of 1 ml of the candidate repellent to the forearm of subjects and exposing the forearm for 2 minutes successively to several thousand caged *Aedes aegypti* and *Anopheles quadrimaculatus* at 20–30-minute intervals until the first bite was obtained.[23] At least two subjects were used for each material. The promising compounds were tested further in a similar manner and also evaluated in paired tests with dimethyl phthalate. The material compared with dimethyl phthalate was applied to one forearm of a subject and dimethyl phthalate was applied to the other forearm. The materials which seemed to be at least equivalent in repellent activity to dimethyl phthalate were submitted for acute toxicity studies (350 ml) by the Food and Drug Administration, Division of Pharmacology,[27] and for further repellency testing (150 ml) in the laboratory and also in the field whenever possible. The candidate repellents

which passed acute toxicity tests, whose commercial production seemed feasible, and which were relatively odorless, nonstaining, and nonirritating were submitted for 90-day subacute toxicity studies (3,1) by the Food and Drug Administration,[27] and for repellency tests (1, 1) in the field against the actual mosquitoes from which protection was desired, especially in the several theaters of war. Testing against different species of mosquitoes is necessary because repellents do not offer uniform protection against all species. It was felt that any compound or mixture which was better than 6-2-2 on the basis of this series of tests would be considered for standardization by the Armed Services.

About 5,000 materials were screened as insect repellents (also tested as insecticides) [29] for application to skin, and, of these, approximately 400 were found to repel *Aedes aegypti* for at least 180 minutes.[29] Approximately 1,600 candidate insect repellents for skin application tests were prepared by the Division 9 contractors on this project, and, of these, about 250 were found to exceed 180 minutes' protection time against *Aedes aegypti*.[5,17–20] Recognition of relationships between insect-repellent effectiveness and chemical structure and volatility [17,19,20] accounted for the much higher percentage of good repellents among the compounds synthesized for repellency tests than from the compounds obtained in random fashion from various sources. In addition to the compounds specifically prepared for the insect repellent program, Division 9 was able to obtain the generous cooperation of several university laboratories in submitting samples of 557 compounds available at these laboratories and not previously tested in Orlando;[21] of these, 24 repelled *Aedes aegypti* for at least 180 minutes in the screening tests.

A total of 196 compounds and mixtures were examined for acute toxicity by skin application to rabbits, and 81 (including several creams and solutions) were found to be neither too toxic nor irritating and were considered worthy of further studies.[27] These materials were carefully considered from the standpoint of repellent effectiveness, relative toxicity and irritancy, odor, staining properties, and acceptability by subjects before selecting the compounds for 90-day subacute studies and field tests overseas.

Table 3 lists the compounds which passed the 90-day subacute tests completed before January 1, 1946. In addition to the compounds listed in Table 3

TABLE 3. Compounds passing 90-day subacute toxicity tests (January 1, 1946).

Orlando Code No.	Name	No. of tests, avg. repellency time in minutes: *a*	*q*	Paired tests, dimethyl phthalate = denominator: *a*	*q*
9†	Indalone ‖,*	104-147	53-41*		
202†	Dimethyl phthalate	1785-258	1807-108		
375†	2-Ethylhexanediol-1,3	180-340	114-55	5-300	5-74
				5-283	5-105
2024†	Propyl cinnamate	8-146§	8-35	2-159	2-34
				2-167	2-128
2026†	Isopropyl cinnamate	96-210	96-118	4-304	4-130
				4-287	4-136
4133†	2-Phenylcyclohexanol	101-383	100-87		
3916†	*cis*(Bicyclo[2,2,1]-5-heptene)-2,3 dicarboxylic acid, dimethyl ester	70-288	70-67	9-308	9-68
				9-273	9-97
5563†	1,2,3,4-Tetrahydro-2-naphthol	43-338	43-52	13-432	13-185
				13-292	13-154
6168‡	Propyl N,N-diethylsuccinamate	45-322	47-76	4-305	4-124
				4-333	4-104
6230‡	Cyclohexyl acetoacetate	41-101§	39-57	4-177	4-128
				4-302	4-144

a = *Aedes aegypti*.
q = *Anopheles quadrimaculatus*.
* The number preceding the hyphen indicates the number of tests performed, the second number gives the average time (in minutes) of the tests.
† Repellency data from Orlando Laboratory, as of June 30, 1945.
‡ Repellency data from Orlando Laboratory, as of September 30, 1945.
§ Longer protection times were obtained in early tests.
‖ Outstanding against *Stomoxys calcitrans*.[29]
¶ Condensation product of methyl oxide and dibutyl oxalate.

SECRET

TABLE 4. Compounds on hand for 90-day subacute toxicity studies (January 1, 1946).

Orlando Code No.	Name	No. of tests, avg. repellency time in minutes: *a*	*q*	Paired tests dimethyl phthalate = denominator: *a*	*q*
1170*	Anisyl alcohol	16 237	16–55	8 208 8–221	8–51 8 71
2145*	Phenoxyethyl acetate	40–178‡	40–50	0–253 0–200	0 58 0 80
2419*	N-sec-Butylphthalimide	16–240	16–51	4–375 4–355	4–77 4–252
3572*	Diisopropyl tartrate	13 288	13–36	5–371 5 340	5–57 5–143
5518†	*p*-*n*-Propoxybenzaldehyde	20–222	34–114	11–220 11–283	16–128 16–163
5533†	4-Anisyl-5-methyl-1,3-dioxane	37–214	33–41	4–353 4 308	4–38 4–112
5542†	Thioglycol diacetate	37–188	39–48	6–173 6–211	6–59 6–121
5567†	Diethyl hexahydrophthalate	55–176‡	53–56	12–254 12–269	12–87 12 156
6133†	Cyclopentyl 1-hydroxycyclohexanecarboxylate	24–236	26–33	2 428 2–371	2–54 2–240
6154†	1,5-Pentanediol dipropionate	27 170‡	31–98	5–281 5–220	7–140 7–146
6216†	Ethyl β-phenylhydracrylate	33 268	31–39	4–405 4–220	4–43 4–122
6252†	Ethyl N,N-dipropylsuccinamate	40–207	40–49	4–304 4–313	4–73 4–153
7000†	5-Ethyl-5-nitro-2-propyl-1,3-dioxane	20 307	20–45	4–150 4–338	4–68 4–102
7021†	Ethyl α-cyanocyclohexaneacetate	38–201	38–48	8 307 8–351	8–64 8–205
7026†	Ethyl β-methyl-β-phenylglycidate	37–165‡	37–53	8–102 8–227	8–78 8–85
7102†	5-Methyl-5-nitro-2-propyl-1,3-dioxane	34–216	34–46	4–273 4–337	4–59 4–144
7145†	N-Butyl-4-cyclohexene-1,2-dicarboximide	26 246	26 48	4 332 4 285	4–49 4–87
10516†	4-Methoxy-3-methylacetophenone	13 281	13–84	5–226 5 248	5–46 5 89

a = *Aedes aegypti*.
q = *Anopheles quadrimaculatus*.
* Repellency data from Orlando Laboratory, as of June 30, 1945
† Repellency data from Orlando Laboratory, as of September 30, 1945.
‡ Longer protection times were obtained in early tests.

the mixtures, 6-2-2 and NMRI 201 (3 parts 1,2,3,4-tetrahydro-2-naphthol and 7 parts 2-phenylcyclohexanol), have passed the 90-day subacute toxicity tests.

Table 4 lists the candidate insect repellents on hand at the Food and Drug Administration for 90-day subacute toxicity studies as of January 1, 1946, the examination of which was still to be completed.

Considerable variation in protection times was obtained with all of the compounds found to possess appreciable repellent activity. Among the factors which have been recognized as determining the protection time of a repellent are species and condition of mosquito, subject, temperature, humidity, condition of the skin, and uniformity of application. Loss by skin absorption is probably the most important factor

in limiting the protection time offered by compounds which do possess repellent properties. The test results obtained in the laboratory with *Aedes aegypti* were qualitatively reproducible, and generally good correlation was obtained with these tests and those in the field against other species, including *Anopheles*.[28]

The laboratory method was refined at the Naval Medical Research Institute at the expense of reducing the capacity for making tests, but the range of repellency times was significantly decreased.[34a] A number of promising repellents as indicated by data developed in Orlando were evaluated on sweating subjects.[34a,b] NMRI 201 (3 parts 1,2,3,4-tetrahydro-2-naphthol, and 7 parts 2-phenylcyclohexanol) gave protection times of 3 7 hours in the laboratory and up to 11 hours in the field, which are longer than 2-phenylcyclohexanol, 1,2,3,4-tetrahydro-2-naphthol, dimethyl phthalate, and 6-2-2 offered alone.[34b] Other mixtures containing derivatives of 2-phenylcyclohexanol and 1,2,3,4-tetrahydro-2-naphthol gave equally good results.[34b]

No repellent effective for at least 12 hours against all species of mosquito and under all conditions was discovered. Nor has a definite path leading to the 12-hour repellent been indicated by these studies. Most of the compounds giving at least 3 hours' protection time have boiling points above 250 C, and none of these is highly nonvolatile. It was demonstrated that certain families of compounds contain more repellents than other families. Compounds containing two groups regarded as conferring repellency when present alone were generally totally inactive. Polyfunctional molecules were more effective than simpler structures. Among the classes of compounds which yielded a substantial number of repellents are amide-esters, N-substituted anilides and araides, 1,3-diols, β-phenylethanols (including 1,2,3,4-tetrahydro-2-naphthol and 2-phenylcyclohexanol) alkoxybenzaldehydes and hydroxyesters.[17,19,20]

Termination of the Division 9 studies on insect repellents shortly after the end of the war with Japan did not permit preparation of samples of several compounds considered worthy of acute and 90-day subacute toxicity studies and further repellency testing. Some toxicity studies are in progress.[27] 1,2,3,4-Tetrahydro-2-naphthol was supplied for extensive field tests and about 140 pounds of this compound have been prepared.[17] Smaller quantities (2 4 pounds) of other promising materials were supplied for field tests by the Army, Navy, the British, Department of Agriculture, and Office of Inter-American Affairs.[17,19,20] Many field data are presumably forthcoming. Repellency data from the field against a variety of mosquitoes are needed in order to evaluate adequately the candidate insect repellents uncovered during the course of this study. The available data indicate that several repellents have been found which are longer-lasting than 6-2-2, although the goal of a 12-hour protection time under any conditions and against all mosquitoes still remains to be attained.

Repellents Tested in Cloth

About 2,500 materials, chiefly solids, were tested in cloth for repellency to indicate their value for impregnation of clothing and face-nets and also for use in solutions, suspensions, and ointments for application to skin.[29] Liquids which failed to pass screening tests for irritancy were tested for repellency in cloth. The test method involved impregnation of women's mercerized cotton hose cut to fit the forearm and exposure of the clothed forearm alternately to caged *Aedes aegypti* and *Anopheles quadrimaculatus*.[29] Exposures were made daily for 2-minute periods. About 10 per cent of the materials screened were repellent for at least 10 days against *Aedes aegypti* and about 2 per cent against *Anopheles quadrimaculatus*. The screening tests were usually terminated at 10 days.

Of the 2,500 compounds, about 500 were synthesized by Division 9 contractors for repellency testing;[5,17–20] and 138 were obtained from university laboratories;[21] 71 were repellent to *Aedes aegypti* for at least 10 days. Among the compounds tested for more than 10 days, N-ethylacetanilide and N-propylacetanilide are outstanding.[17] They were still repellent to *Aedes aegypti* after 35 days, and in 20 per cent solutions in dimethyl phthalate have passed acute toxicity tests.

Use of the better solid repellents in the form of solutions, suspensions, and ointments for skin application remains to be adequately evaluated. Several of the solid repellents in dimethyl phthalate solution offer longer protection times in skin application tests than dimethyl phthalate alone. Impregnation of repellents in clothing and in both close- and wide-mesh nets have rendered these articles repellent for periods ranging from 1 week to 5 months.[17,29] However, insufficient repellency and toxicity data have been obtained to indicate which of the materials examined to date are the best for impregnation of clothing and nets.

42.6 MITICIDES — FIXATION ON COTTON FABRIC

The control of scrub typhus, which is transmitted by mites, was a serious problem to the Armed Services in the Pacific and the China-Burma-India theaters. No specific treatment for the disease was available, but protection was obtained by impregnating clothing to be worn in the endemic areas with dimethyl phthalate, which had been found to possess miticidal action. The easy removal of dimethyl phthalate from clothing by rinsing in water indicated need for a miticide more fast to clothing or means to bind dimethyl phthalate more firmly to fabric.

A variety of materials were studied for their fixative power on dimethyl phthalate in fabrics in order to increase the resistance of the impregnated dimethyl phthalate to leaching by water and laundering.[18] The most promising binders found during these studies were polyvinyl acetate-chloroparaffin and polyvinyl acetate. Fabrics impregnated with compositions containing dimethyl phthalate and these binders were still miticidal after a 48-hour rinse and one laundering, whereas dimethyl phthalate alone is removed from clothing by one laundering or in less than 30 minutes by rinsing in cool water.

Miticides have been discovered which, when impregnated in clothing without binders, are considerably more resistant to removal than even the aforementioned compositions.[29] If the best of these miticides are found not to last as long as the clothing itself, their use in conjunction with binders should be investigated.[18,29]

42.7 RODENTICIDES

New Rodenticides

During the fall of 1943 a representative of the U. S. Department of Interior, Fish and Wildlife Service, Economic Investigations Laboratory, requested the cooperation of NDRC Division 9 on a research program to find new rodenticides superior to those available at the time. This request was made primarily because it was felt that the considerable amount of toxicity data which had been developed within the Division in connection with studies on candidate chemical warfare agents might indicate new rodenticides more effective than the standard rodenticides.

After a consideration of the requirements for a rodenticide as indicated by the Fish and Wildlife Service representative and of the toxicity data, a number of compounds were recommended by this Division for testing.[30] Samples of these compounds and others were requested by the Fish and Wildlife Service, and samples of 98 compounds were furnished for screening tests. Among the compounds suggested by this Division was sodium fluoroacetate (1080),[30] which proved to be an outstanding rodenticide. About 1,000 pounds of this compound was supplied [7] for field tests by the Fish and Wildlife Service, Army, Navy, U. S. Public Health Service, and other organizations. The preparation, physical and chemical properties, and toxicology of sodium fluoroacetate are summarized in Chapter 10. The results of the field tests are reported elsewhere.[31]

Several compounds were found to be slightly more toxic to rodents (Chapter 10) than sodium fluoroacetate; however, the latter is easier to prepare and its toxicity is more than adequate. Samples of 2-chloro-4-dimethylamino-6-methylpyrimidine (Castrix giftkorner) [24] and sodium *p*-dimethylaminobenzenediazosulfonate,[23] which were regarded favorably in Germany as rodenticides, were prepared. Screening tests for toxicity to rats indicated that these compounds are less effective rodenticides than sodium fluoroacetate; however, the toxicity data warranted the preparation of sufficient quantities for field tests.

Chemical Assay of Red Squill

Lots of red squill powder are usually tested for toxicity to rats before being formulated into baits for use as rat poisons. Assay is necessary because different lots vary considerably in toxicity. The bioassay procedure is costly and time-consuming, and the results seem to vary markedly with the strain, sex, and size of the rats used.

A limited search [22] was made for chemical methods that might be suitable for a rapid and reliable assay of the principle in red squill which is toxic to rodents.[40] Highly toxic fractions were isolated from samples of red squill; however, attempts to correlate the results of quantitative analytical procedures applied to the various fractions and samples with bioassay determinations [22] were not successful.

Chapter 43

SYNTHESIS OF ANTIMALARIAL INTERMEDIATES AND DRUGS

By *Arthur C. Cope*

43.1 INTRODUCTION

In July 1944 work in seven laboratories of the National Defense Research Committee [NDRC], Section 9.2, was diverted wholly or in part from chemical warfare problems to synthesis of antimalarial intermediates and drugs. Authorization for the NDRC contractors to participate in the malaria program of the Committee on Medical Research [CMR] was arranged by representatives of the two agencies. Through this arrangement the experience and manpower of the laboratories concerned furnished an added impetus to the malaria program, particularly by synthesis of some of the intermediates needed for preparation of the more promising drugs selected for clinical trial. At the same time the plan enabled the NDRC laboratories to retain their personnel and remain in a stand-by condition which would permit immediate resumption of work on chemical warfare problems in the event of initiation of chemical warfare. On September 1, 1945, the remaining Section 9.2 contracts concerned with the malaria program were transferred to CMR, and completed their work (terminating December 31, 1945, February 28, or May 31, 1946) under CMR contracts.

The following university laboratories participated in the program through contracts with the Office of Scientific Research and Development, as listed: University of Wisconsin (OEMsr-304, OEMcmr-567); State University of Iowa (OEMsr-223, OEMcmr-564); University of Illinois (OEMsr-300, OEMcmr-570); Iowa State College (OEMsr-97, OEMcmr-565); University of Nebraska (OEMsr-85, OEMcmr-566); Northwestern University (OEMsr-[illegible]5, OEMcmr-563); Indiana University (OEMsr-195).

Under these contracts a total of 95 antimalarial intermediates and 12 drugs were synthesized, in quantities varying from 1 g to 12 kg. In addition, process development work was conducted on the synthesis of several compounds as a preliminary to their preparation on a large laboratory, pilot plant, or manufacturing scale. Details of the chemical work completed under the program appear in progress reports which are listed in the Bibliography. Much of the work is to be published in the open literature, where it can be located through reference to the official investigators as co-authors. The following section comprises a list of the compounds that were prepared.

43.2 INTERMEDIATES AND DRUGS PREPARED

1. *References 10 and 15.*

Compound	Amount
γ-Diethylaminopropylamine	5,241 g
cis-δ-Decalone	218 g
Spermine tetrahydrochloride	45.6 g
Spermidine trihydrochloride	12.5 g
Di-*n*-nonylamine	4,179 g
n-Nonylamine	550 g
ac. β-Tetralone	370 g
2-Diethylaminomethyl-4-aminophenol hydrochloride	81 g
Tetrahydroanthracene	575 g
Methylisopropylamine	1,105 g

2. *References 1, 8, and 12.*

Compound	Amount
Tetrahydrophenanthrene-9-aldehyde	1,343 g
1-Diethylamino-3-aminobutane	1,091 g
β-Diethylaminoethylamine	2,094 g
9-Acetylphenanthrene	1,150 g
9-Acetyl-tetrahydrophenanthrene	7,015 g
Phenanthrene-9-aldehyde	822 g
3-Chloro-5-nitrobenzoic acid	2,012 g
4-Chloro-1-acetonaphthone	500 g
4-Chloro-1-naphthaldehyde	731 g
δ-Cyclopentylvaleric acid	500 g
Ethyl cyclohexanone-2-carboxylate	1,191 g
Nitrosomethyl urea	10,198 g
2-Cyclohexyl-4-*tert*-butylphenol	1,500 g
6-Methoxyquinoline	3,434 g
2-Chloro-4-aminoanisole	200 g
6-Aminohexanol-1	71 g
Mono-*tert*-butylamine	741 g
4-Chloro-1-naphthoic acid	100 g
5,7-Dichloroisatin	0.5 kg
Meconic acid	200 g
Ethyl hydrogen adipate	1,230 g
Ethyl hydrogen sebacate	800 g

3. *References 9 and 10.*

Compound	Amount
Ethyl ethoxymethylene malonate	12,131 g
4,7-Dichloroquinoline	10,149 g
Di-*n*-octylamine	7,987 g
2-Phenyl-4,7-dichloroquinoline	300 g
3-Bromophenanthrene	100 g
2-Phenyl-4-chloro-6-methoxyquinoline	122.8 g
4-Amino-7-chloroquinoline	884 g

3. *(Continued).*

Compound	Amount
2-Phenyl-4-hydroxy-7-chloroquinoline	10 g
2-Phenyl-4-hydroxy-6-methoxyquinoline	10 g
Di-*n*-hexylamine	5 kg
2-Amino-4-chlorobenzoic acid	130 g
3-Diethylaminopropylchloride	9,200 g
3-Diethylaminopropylchloride hydrochloride	974 g
N-Benzoyl pipecolinic acid ethyl ester	211 g
Pipecoline acid ethyl ester hydrochloride	710 g
7-Chloro-4-(1-ethyl-4-piperidylamino)-quinoline (SN 13,425)	668 g
5,8-Quinoline quinone	2 g
5,8-Dihydroxy quinoline	2.1 g
5,8-Diacetoxy quinoline	2.4 g
4,8-Dihydroxyquinaldic acid	1.9 g
8-(6-Diethylaminohexylamino)-5-(2-hydroxyethoxy)-6-methoxyquinoline	

4. *References 5 and 13.*

Compound	Amount
m-Anisidine	3,041 g
Picolinic acid	2,516 g
Ethyl formylphenylacetate	3,010 g
2-Chloro-3-aminotoluene	300 g
3-Diethylamino-2-hydroxypropylamine	5,017 g
1-Diethylamino-2,3-epoxypropane	200 g
8-Hydroxycinchoninic acid	60 g
6,7-Methylenedioxy-2-phenylquinoline-4-carboxylic acid	[illegible] g
Cinchoninic acid	[illegible] g
2-Chloro-6-nitroquinoline	197 g
6-Nitro-8-chloroquinoline	200 g
Ethyl γ-bromocrotonate	512 g
2-Phenyl-6-methoxycinchoninic acid	1,200 g
5,7-Dichloroisatin	505 g
γ-2-Piperidylpropyl chloride	502 g
Quininic acid	304 g
5,6-Dimethoxy-8-nitroquinoline	3,178 g
4-Aminoveratrole	500 g
α-(3-Diethylaminopropyl)-6-methoxy-2-phenyl-4-quinolinemethanol (SN 12,858)	11.5 g
6,8-Dichloro-α-(dibutylaminomethyl)-2-(2-pyridyl)-4-quinolinemethanol (SN 14,143-4)	10 g
γ-Diethylamino-α-hydroxybutyronitrile	4,300 g
1-(6-Methoxy-2-phenyl-4-quinolyl)-1-propanone	4 g
8-(2,5-dimethyl-1-pyrryl)-5,6-dimethoxyquinoline	6 g
α-(3-Diethylaminopropylmercaptomethyl)-6-methoxy-2-phenyl-4-quinolinemethanol dihydrochloride	4 g
α-(2-Diethylaminomethylmercaptomethyl)-6-methoxy-2-phenyl-4-quinolinemethanol dihydrochloride	10 g

5. *References 2, 4, and 14.*

Compound	Amount
Ethyl oxalopropionate	14 lb
Quinoline-4-aldehyde	700 g
4-Chloro-2-nitrobenzaldehyde	63 g
1-(4-Diethylamino-1-methylbutylamino)-benzo(f)quinoline diphosphate (SN 11,020)	15 g
4-(4-Diethylamino-1-methylbutylamino)-benzo(h)quinoline diphosphate monohydrate (SN 11,021)	15.3 g
4-Diethylaminobutylamine	105 g
5-Nitro-8-chloroquinoline	1 kg
2-Bromo-3-nitrobenzoic acid	2 kg
β-Hydroxy-β'-aminoethyl ether	50 g
6-Methoxyquinoline-4-aldehyde	105 g

6. *References 6 and 11.*

Compound	Amount
Dibenzylamine	500 g
Ethyl cinchoninate	1,548 g
o-Nitrobenzaldehyde	1,768 g
p-Chlorophenylacetic acid	2,065 g
Ethyl 6-chlorocinchoninate	500 g
6-Chloroveratrole	50 g
3,6-Dichloroveratrole	50 g
4-Methoxy-6-chloroveratrole	50 g
5-Methyl-3,6-dichloroveratrole	50 g
6-Chloro-1-naphthaldehyde	83.7 g
p-Nitroacetophenone	140 g
m-Hydroxybenzaldehyde	288 g
o-Nitroacetophenone	714 g
Homophthalic acid	500 g
1,4-Dimethoxy-2-butyne	250 g
2,4-Dimethylquinoline	103 g
8-(6-Allylaminohexylamino)-6-methoxyquinoline	18.9 g
8-(6-Diallylaminohexylamino)-6-methoxyquinoline	18.2 g

7. *References 3 and 7.*

Compound	Amount
5-Aminoisoquinoline	1.5 kg
1-Chloro-5-nitroisoquinoline	50 g
1,4-Dichloroisoquinoline	20 g

Two investigations directed primarily toward development of synthetic methods complete the citation of work undertaken under this program. They were:

1. Investigation of the synthesis of plasmochin by reductive alkylation of 8-amino-6-methoxyquinoline with noval ketone and noval ketone diethylacetal.[10,15]

2. Development of an improved method for preparing 2-phenyl-6-methoxy-4-quinolinecarbinols.[5,13]

GLOSSARY

AC. Hydrocyanic acid.

ACTIVE CHLORINE. Chlorine capable of chlorinating H.

ADAMSITE. Diphenylamine chlorarsine.

AEROSOL OT. Sodium dioctylsuccino sulfate.

AF-1, MFA, TL 551, T-1202. Methyl fluoroacetate.

A/G. Albumin: Globulin plasma protein ratio.

A.G. No. 5. Ointment having following composition: 25 per cent impregnite E, 20 per cent diethyl phthalate, 10 per cent hydrogenated whale oil, 4 per cent sodium stearate, 2 per cent potassium stearate, and 39 per cent water.

A.G. No. 6. Ointment similar to A.G. No. 5, in which hydrogenated whale oil is replaced by hydrogenated peanut oil.

ALKANOL WXN. Sodium hydrocarbon sulfonate.

AMMONYX 00. Oleyl dimethylamine oxide. (Onyx Oil and Chemical Co.)

AMOLOID LV. A low viscosity ammonium alginate.

AR-16. *See* TL 1217.

AREA DOSE. Expressed as milligrams per square meter it is numerically equivalent to the product of *Ct* (in milligram minutes per cubic meter) and the wind speed (in meters per minute). Not to be identified with the ground contamination.

ARKOPAL N-100. Dibutylphenylphenol, sodium disulfonate.

ARMY CLOTH. A cotton twill fabric purchased by the Navy Department for the preparation of CC-2 impregnated permeable protective garments.

ATP. Adenosine triphosphate.

AV. British anti-gas impregnite (N,2,4-trichlorobenzanilide).

B-1. *P*-Nitrophenylazo-(β-napthylamine).

BAL. 1,2-Dimercaptopropanol.

BBC. α-Bromobenzyl cyanide.

BENZYL H. Benzyl β-chloroethyl sulfide.

bp^p. Boiling point in C at p mm./Hg.

BREAK TIME. *See* protective time.

BUTYL-H. Butyl (β-chloroethyl) sulfide.

CAPACITY. Amount of vesicant gas per square centimeter applied to fabric to reduce retention efficiency to given value.

CARBITOL. Monoethyl ether of diethylene glycol.

CARLISLE CARBON. Activated carbon prepared by the Crown-Zellerbach Company.

CC-1. Same as CC-2.

CC-2. N,N'-Dichloro-N,N'-*bis*(2,4,6-trichlorophenyl)-urea.

CEVS. β-Chloroethyl β'-chlorovinyl sulfide.

CG. Phosgene.

CH. β-Chloroethyl β-hydroxyethyl sulfide.

CHOLINERGIC. Effects produced on parasympathetic nervous system similar to those produced by acetyl choline.

CK. Cyanogen chloride.

CMR. Committee on Medical Research.

CN. Chloroacetophenone.

CP. Chloropicrin containing approximately 40 per cent chlorine.

Ct. Product of concentration in milligrams per cubic meter and time of exposure in minutes.

CWS. Chemical Warfare Service.

CYAN DA. Diphenylamine cyanoarsine.

DANC. Decontaminating agent, noncorrosive, consisting of a solution of 1 part by weight of RH-195 in 15 parts of TCE.

DAP. Diaminopropylene.

DAXAD 11. Naphthalene formaldehyde sodium sulfonate.

DB-3. 4-(*p*-Nitrobenzyl)pyridine, a reagent for detecting H and other β-chloroethyl compounds.

DBT. Di-*p*-biphenyl-thiocarbazone.

DC. Diphenylcyanoarsine.

p,p'-DDD. 1,1-Dichloro-2,2-*bis*(*p*-chlorophenyl)-ethane.

DDT. 1-Trichloro-2,2-*bis*(*p*-chlorophenyl)-ethane (commercial product).

m,p'-DDT. 1-Trichloro-2-*m*-chlorophenyl-2-*p*-chlorophenyl-ethane.

o,p'-DDT. 1-Trichloro-2-*o*-chlorophenyl-2-*p*-chlorophenyl-ethane.

p,p'-DDT. 1-Trichloro-2,2-*bis*(*p*-chlorophenyl)-ethane (pure compound).

DECONTAMINANT 40. Trichloroisocyanuric acid.

DH. *See* H.

DHX. *See* H.

DIRECTIVE 162. Edgewood Arsenal directions for the carrying out of an empirical test for measuring the H resistance of permeable fabrics.

DM. Adamsite.

DNB. 4-(*o,p*-Dinitrobenzyl)-pyridine.

DP. Trichloromethyl chloroformate (diphosgene).

DPE. Diphenyl ether.

DPF. *See* PF-3.

DPT. Di-*o*-phenoxyphenyl thiocarbazone.

DPU. Diphenylurea.

$d_{t_2}^{t_1}$. Specific gravity at t_1 C in reference to water at t_2 C.

DTH. *See* BAL.

DUPONOL ME. Sodium dodecyl sulfate (commercial grade).

DURATION OF PROTECTION. Duration of exposure (usually in toxic chamber) in which a garment provides protection.

EA. Edgewood Arsenal.

ED. Ethyl dichlorarsine.

EDS. Effective drop size (British).

ETHYL S. *See* HN1.

F-5, Z, 1120, TL 70, T-1377. Disulfur decafluoride.

FE, TL 741, T-1004. β-Fluoroethanol.

H. *bis*(β-Chloroethyl) sulfide, mustard gas.

H^a. Radioactive H.

HAWORTH COMPOUND. *See* T-1708.

HAWORTH ISOMER. *See* TL 1216.

HBT. Herringbone twill.

H, DH, DHX. *bis*(β-Chloroethyl) sulfide.

H-ITG. β-Chloroethyl-β-[*bis*(β-hydroxyethyl)-sulfonium]-ethyl sulfide chloride.

H-2TG, TL 510. *bis[bis-(β-Hydroxyethyl) sulfoniumethyl]*.

HMT. Hexamethylene tetramine.

HN1, TL 329, T-1790, 1149, ethyl S. Ethyl-*bis(β-chloroethyl)*amine.

HN2, TL 146, T-1024, 1130, S. Methyl-*bis(β-chloroethyl)*amine.

HN3, TL 145, T-773, 1070. *tris(β-Chloroethyl)*amine.

HS. *bis-(β-Chloroethyl)* hexasulfide.

H SULFONE. *bis(β-Chloroethyl)* sulfone.

IMPREGNITE E. *N,2,4-Trichlorobenzene*

INDALONE. Condensation product of mesityl oxide and dibutyl oxalate. (Kilgore Mfg. Co.)

6-2-2 INSECT REPELLENT. 6 parts dimethyl phthalate, 2 parts 2-ethylhexanediol-1,3, and 2 parts Indalone.

ISOPROPYL S. *See* TL 301.

KALYE-A. An inorganic detergent containing 75 per cent sodium metasilicate and 25 per cent tetrasodium pyrophosphate. Made by the Rumford Chemical Company.

K3-10. *N-(β-Chloroethyl)-N-nitrosocarbamate.*

KOPAN. An alkali soluble zinc cellulose.

L (Lewisite). *β-Chlorovinyldichloroarsine.*

LD_{50}. Lethal dosage, *isopropyl-bis(β-chloroethyl)*amine.

LE-100. *See* MCE.

MAN "BREAK". Failure of protective clothing to continue to protect single subject.

MCE, TABUN, LE-100, TL 1378, T-2104. Ethyl dimethylamidocyanophosphate.

MD. Methyldichloroarsine.

METHYL-H. Methyl-(β-Chloroethyl) sulfide.

MFA. Methyl fluoroacetate.

MFI, SARIN, T-144, TL 1618, T-2106. Isopropyl methanefluorophosphonate.

MICRONIZING PROCESS. A process for producing finely-ground material.

MMD. Mass median diameter.

MP. Melting point.

M-1 EYE SOLUTION. 5.6 per cent solution of BAL in highly purified ethylene glycol.

M-1 PROTECTIVE OINTMENT. Ointment having following composition: 25 per cent dichloramine-T, 65 per cent triacetin, and 10 parts cellulose acetate butyrate.

M-2 PROTECTIVE OINTMENT. Ointment similar to M-1, but containing chloramine-T.

M-3 PROTECTIVE OINTMENT. Ointment similar to M-1, but containing dichloramine-P.

M-4 PROTECTIVE OINTMENT. Later designation applied to M-1 Protective Ointment.

M-5 PROTECTIVE OINTMENT. Same as S-330 Protective Ointment.

M-1, T of O. Theater of Operation plant for the impregnation of garments with a tetrachloroethane solution of a chloramide impregnite.

M-2, T of O. Theater of Operation plant for the impregnation of garments with a water dispersion of a chloramide impregnite.

μg. Microgram, gamma.

MP-646 Sodium hydrocarbon sulfonate.

MSA. Mine Safety Appliances Co.

NACCONOL NR. An alkyl naphthalene sulfonic acid sodium salt.

NMD. Number median diameter.

NMRI 201 INSECT REPELLENT. 3 Pts 1,2,3,4-tetrahydro-2-naphthol and 7 parts 2-phenylcyclohexanol.

NPN. Nonprotein nitrogen.

NRL. Naval Research Laboratory.

n_D^t. Refractive index at t°C.

N-44 CARBON. An obsolete type of activated carbon produced in the Chemical Warfare Service's Fostoria, Ohio plant by the National Carbon Company.

N-182 CARBON. A certain type of activated carbon produced in the Chemical Warfare Service's Fostoria, Ohio plant by the National Carbon Company.

OD. Olive drab.

OSRD. Office of Scientific Research and Development.

PCC CARBON. Activated carbon produced by the Pittsburgh Coke and Chemical Company. (Also PCL)

PD. Phenyldichloroarsine.

PENTAMUL 87. Pentaerythritol soya bean fatty acid monoester. (Heyden Chemical Corp.)

PENTAMUL 126. Pentaerythritol monooleate. (Heyden Chemical Corp.)

PER-CLENE. Tetrachloroethylene.

PERFLUORO COMPOUND. A substance in which *all* the hydrogen atoms attached to carbon have been replaced by fluorine. Use of the prefix *perfluoro-* in naming compounds is recommended because of the awkwardness of the Geneva nomenclature. Thus, perfluoro-1,3-butadiene is preferred over 1,1,2,3,4,4-hexafluoro-1,3-butadiene, and perfluoro-1,4-dichlorobutane is simpler than 1,1,2,2,3,3,4,4-octafluoro-1,4-dichlorobutane. The Greek letter φ is sometimes used as an abbreviation for perfluoro. Thus, the compounds mentioned may most simply be identified as φ-butadiene and φ-1, 4-dichlorobutane.

PF-1, TL 311, T-1035. Dimethyl fluorophosphate.

PF-3, TL 466, T-1703, 1152. Diisopropyl fluorophosphate.

PHI-O-SAL. Sodium ricinoleic sulfonate.

PHOSGENE OXIME. Dichloroformoxime.

PHV. Pinhead vesicles.

PR. Protein.

n-PROPYL S. *See* TL 481.

PROSTIGMINE. Carbamic acid, N,N-dimethyl-3-dimethylaminophenyl ester methosulfate.

PROTECTIVE TIME. Elapsed time prior to penetration of permeable fabric as measured by laboratory tests.

PVA. Polyvinyl alcohol.

Q. 1,2-*bis(β-Chloroethylthio)*ethane. Sesqui mustard.

RETENTION EFFICIENCY. 100 minus the per cent of vesicant gas applied to fabric which penetrates.

RH. Relative humidity.

RH-185. 1,3-Dichloro-5,5-dimethylhydantoin.

RHOPLEX WC-9. A copolymer of ethyl acrylate and methyl acrylate dispersed in a 5 per cent aqueous emulsion.

S. *See* HN2.

S^{35}. Radioactive sulfur.

SALCOMINE. Salicylaldehyde ethylenediimine cobalt.

SARIN. *See* MFI.

SB. Substances arising in and imparting unique pharmacological properties to aged solutions of (A) HN2, and (B) HN2 chlorohydrin. [(A) *methyl-β-hydroxyethylamine*; (B) *1-methyl-1-(β-hydroxyethyl)-ethyleniminonium chloride.*]

SB-8. *See* TL 380.

S.D. TEST. *See* Spotted Dick.

Solvesso No. 1. Hydrogenated naphtha, bp 93-135 C. (Standard Oil of New Jersey.)

SP-315. Alkali metal petroleum sulfonate. (Stanco, Inc.)

Spotted Duck Test. British test for estimating protective properties of permeable fabrics.

Spot "Break". Complete failure of protective clothing due to exhaustion of protective capacity.

S-210. 1,1'-Methylene-*bis*-(3-chloro-5,5-dimethylhydantoin).

S-221. 1,3-Dichloro-5,5-diphenylhydantoin.

S-222. 1,3-Dichloro-5,5-diphenyl-2-iminohydantoin.

S-300. 1,3-Dichloro-5,5-diphenyl-2-chloroiminohydantoin.

S-328. 7,8-Diphenyl-1,3,4,6-tetrachloroglycoluril.

S-330. 7,8-Diphenyl-1,3,4,6-tetrachloro-2,5-diiminoglycoluril.

S-426. 7,8-Diphenyl-1,3,4,6-tetrachloro-2,5-*bis*(chloroimino)-glycoluril.

S-436. 2,4-*bis*(Dichloroamino)-6-phenyl-1,3,5-triazine.

S-461. 7,8-Dimethyl-1,3,4,6-tetrachloroglycoluril.

S-330. Protective Ointment. Ointment having following composition: 25 per cent S-330, 4 per cent cellulose acetate butyrate, 9 per cent titanium dioxide, 9 per cent magnesium stearate, 52 per cent triacetin, 0.8 per cent Sulfanthrene Brown G, and 0.2 per cent Monastral Fast Green G.

T. *bis*(β-Chloroethylthioethyl) ether.

T-144. *See* MF1.

T-773. *See* HN3.

T-1024. *See* HN2.

T-1035. *See* PF-1.

T-1036. *See* TL 345.

T-1123. *See* TL 1217.

T-1202. *See* AF-1.

T-1317. *See* F-5.

T-1377. *See* F-3.

T-1703. *See* PF-3.

T-1708. *See* TL 1071.

T-1790. *See* HN1.

T-1824. Evans blue dye.

T-1835. *See* TL 1206.

T-1840. *See* TL 941.

T-1904. *See* FE.

T-1957. *See* 1080.

T-2002. *See* TL 702.

T-2104. *See* MCE.

T-2106. *See* MF1.

T-2109. *See* TL 1620.

T of O. Theater of Operation.

Tabun. *See* MCE.

Tabun XNO. Naphthalene formaldehyde sodium sulfonate.

TCA. Trichloroaniline.

TCE. Tetrachloroethane.

TG. Thioglycol [*bis*(β-hydroxyethyl) sulfide].

TL 70. *See* F-5.

TL 138. Sulfur hexafluoride.

TL 145. *See* HN3.

TL 146. *See* HN2.

TL 301. Isopropyl S. Isopropyl-*bis*(β-chloroethyl)amine.

TL 311. *See* PF-1.

TL 329. *See* HN1.

TL 345, T-1036. Diethyl fluorophosphate.

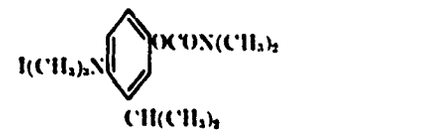
TL 406. *See* PF-3.

TL 481. *n*-propyl S. Propyl-*bis*(β-chloroethyl)amine.

TL 510. *See* H-2TG.

TL 551. *See* AF-1.

TL 590, SB-8. (3-Isopropyl-4-dimethylaminophenyl)-N,N-dimethylcarbamate methiodide.



TL 741. *See* FE.

TL 702, T-2002. *bis*(Dimethylamido) phosphoryl fluoride.

TL 880. *See* 1080.

TL 941, T-1840. Dicyclohexyl fluorophosphate.

TL 1071, T-1708, "Haworth Compound." (2-Methyl-5-dimethylaminophenyl)-N-methylcarbamate methiodide. *See* text, page 204.

TL 1185. *See* text page 204.

TL 1190. *See* text page 204.

TL 1188. *See* text page 204.

TL 1216, "Haworth Isomer." (4-Methyl-3-dimethylaminophenyl)-N-methylcarbamate methiodide. *See* text page 204.

TL 1217, T-1123, AR-16. *m*-Diethylaminophenyl-N-methylcarbamate methiodide. *See* text page 204.

TL 1235. *See* text page 204.

TL 1266, T-1835. Di-*sec*-butyl fluorophosphate.

TL 1299. *m*-Diethylaminophenyl-N-methylcarbamate methochloride. *See* text page 204.

TL 1317. *See* text page 204.

TL 1453. *See* text page 204.

TL 1578. *See* MCE.

TL 1618. *See* MF1.

TL 1620, T-2109. Isopropyl ethanefluorophosphonate.

T of O. Theater of Operation.

Trichloro-II. 1, 2,2'-Trichlorodiethyl sulfide.

Trilons. German liquid preparations (MCE) of PF series. Alkyl cyanamidophosphates and alkyl fluorophosphonates.

Triton 770. Sodium aryl alkyl polyether sulfate.

Triton X-100. Polyethyleneglycol octylphenyl ether. (Rohm & Haas Co.)

TU. Toxicity unit representing a value for the dose corresponding to a mean survival time of 24 hr. (See Section 12.5.1.)

"Tuck" Cells. A kind of "irritation" cell.

UTCL. University of Chicago Toxicity Laboratory.

V. 1-Methyl-1-(β-hydroxyethyl) ethyleniminonium picrylsulfonate.

VMD. Volume median diameter.

vol'. Saturation concentration (volatility) in mg per liter at *t* C.

vp'. Vapor pressure in mm Hg at *t* C.

W. Ricin.

Wheelerize. Treatment of activated carbon for use in canisters with chemicals to increase protection against nonpersistent agents.

XNCC-2. Micronized CC-2.

XNCC-3. CC-2 micronized with ZnO 100 10.

Z. *See* F-5.

Z of I. A "Zone of Interior" plant for the impregnation of garments with a tetrachloroethane solution of a chloroamide impregnite. (CWS.)

I. 1-Methyl-1(β-chloroethyl) ethylenimonium chloride.
II. 1-Methyl-1-(β-chloroethyl) ethylenimonium picrylsulfonate.
III. Methyl-β-chloroethyl-β-hydroxy-ethylamine hydrochloride.
IV. 1-Methyl-1-(β-hydroxyethyl) ethylenimonium chloride.
V. 1-Methyl-1-(β-hydroxyethyl) ethylenimonium picrylsulfonate.
1070. *See* HN3.
1080, TL 869, T-1957. Sodium fluoroacetate.
1120. *See* F-5.
1130. *See* HN2.
1140. *See* HN1.
1152. *See* PF-3.

BIBLIOGRAPHY

Numbers such as Div. 9-323.2-M1 indicate that the document listed has been microfilmed and that its title appears in the microfilm index printed in a separate volume. For access to the index volume and to the microfilm, consult the Army or Navy agency listed on the reverse side of the half-title page.

EXPLANATORY NOTES FOR BIBLIOGRAPHY

The usual sequence in which the references for each chapter are listed is as follows:

OSRD REPORTS

1. Formal. Listed systematically according to number.
2. Informal. Listed according to the contract under which they were prepared.

The contracts are arranged as follows:

a. NDCrc — contracts in order of increasing number.
b. OEMsr — contracts in order of increasing number.
c. OEMcmr — contracts in order of increasing number.

3. Miscellaneous. All items originating with contractors are arranged as in the case of formal reports. Other items (e.g., those written by Division Members or Technical Aides) follow.

UNITED STATES ARMY REPORTS

1. Chemical Warfare Service (CWS). In most instances the numerous series of reports are listed in the following order:

a. CMTR (Captured Matériel Technical Report).
b. CMTR-MIT (Captured Matériel Technical Report) from the Chemical Warfare Service Development Laboratory at the Massachusetts Institute of Technology.
c. DPGFPR (Dugway Proving Ground Field Progress Report).
d. DPGMR (Dugway Proving Ground Memorandum Report).
e. DPGSR (Dugway Proving Ground Special Report).
f. EACD (Edgewood Arsenal Chemical Division Report).
g. EAMRD (Edgewood Arsenal Medical Research Division Report).
h. EATR (Edgewood Arsenal Technical Report).
i. Field Laboratory Memoranda.
j. HR(EA). (Edgewood Arsenal Hospital Report.)
k. MD(EA)MR. [Medical Division (Edgewood Arsenal) Memorandum Report.]
l. MD Rept., or Med. Div. Rept. [Medical Division (Edgewood Arsenal) Report.]
m. MIT-MR (Memorandum Report from the Chemical Warfare Service Development Laboratory at the Massachusetts Institute of Technology).
n. MRI(DPG) Rept. [Medical Research Laboratory (Dugway Proving Ground) Report.]
o. MRI(EA) Rept. [Medical Research Laboratory (Edgewood Arsenal) Report.]
p. SJ Rept. (San José Project Report.)
q. TDMR [Technical Division (Edgewood Arsenal) Memorandum Report].
r. TRLR [Toxicological Research Laboratory (Edgewood Arsenal) Report].
s. Chemical Laboratory Company Reports.
t. DPG Inf. Rept. (Dugway Proving Ground Informal Report.)
u. MD Inf. Rept., or Med. Div. Inf. Rept. (Medical Division Informal Report.)
v. MRI(DPG) Inf. Rept. [Medical Research Laboratory (Dugway Proving Ground) Informal Report.]
w. MRI(EA) Inf. Rept. [Medical Research Laboratory (Edgewood Arsenal) Informal Report.]
x. TRI(EA) Inf. Rept. [Toxicological Research Laboratory (Edgewood Arsenal) Informal Report.]
y. Chemical Warfare Service Contractors' reports.
z. Miscellaneous Chemical Warfare Service Reports and Memoranda.

2. Miscellaneous United States Army Reports.

UNITED STATES NAVY REPORTS

1. Bureau of Aeronautics.
2. Naval Research Laboratory. The formal reports bear a P-number and are listed first. They are followed by letters and memoranda bearing Navy identification numbers and dates.

UNITED STATES PUBLIC HEALTH SERVICE REPORTS

UNITED STATES DEPARTMENT OF INTERIOR REPORTS

OFFICE OF STRATEGIC SERVICES REPORTS

UNITED STATES—UNITED KINGDOM REPORTS

Most of these originated with the Project Coordination Staff (PCS) at Edgewood Arsenal. In some chapters they are listed as Chemical Warfare Service Reports because of the administrative affiliation of the Staff with the Chief of the Service.

BRITISH REPORTS

1. Chemical Defence Experimental Station (Porton). The several series of reports are listed in the following order:

a. Porton Memoranda.
b. Porton Reports.
c. Porton Departmental Reports.
d. Ptn. Porton "letters" identified by a number and followed in parentheses by a letter and a second number. The first number is a general reference number; the letter

indicates the year in which the "letter" was written; the second number is a specific reference number for the "letter."

2. Research Establishment, Sutton Oak (S.O.).
3. Extramural Research. The reports are listed according to institution and principal investigator. They are usually characterized by a report number assigned by the investigator and or a diagnostic British Chemical Board reference consisting of a letter indicating the year in which the report was circulated (e.g., W = 1942; Y = 1943) followed by a number.
4. Miscellaneous.

CANADIAN REPORTS

1. Experimental Station, Suffield, Alberta. The reports are of several series, including Suffield Technical Minutes, Suffield Reports, and Suffield Field Reports.
2. National Research Council Laboratories, Ottawa.
3. Chemical Warfare Laboratories, Ottawa.
4. Extramural Research.
5. Miscellaneous.

AUSTRALIAN REPORTS

Most of these originated at the Chemical Defence Board, Research and Experimental Station, Innisfail, Queensland, or the Australian Field Experimental Station, Proserpine, Queensland, and bear the designation CD (Australia) Report or Note.

INDIAN REPORTS

Most of these originated at the Chemical Defence Research Establishment, Rawalpindi, and bear the designation CDRE (India) Report or Note.

OPEN LITERATURE

References to books and journal articles are arranged alphabetically by author.

IDENTIFICATION SYMBOLS

TL numbers are Toxicity Laboratory (University of Chicago) code numbers.

T numbers are the British and Canadian code.

AR numbers refer to the Aeschlimann and Reinert publication (Reference 49 of Chapter 13.)

SB numbers refer to the Stevens and Beutel publication. (Reference 53 of Chapter 13.)

Chapter 1

UNITED STATES—UNITED KINGDOM REPORTS

1. Project Coordination Staff (Edgewood Arsenal) Rept. No. 9. *Résumé of Recent Knowledge on the Technical Aspects of Chemical Warfare in the Field*, May 17, 1945.
2. *The Relative Effectiveness of HE and CW Munitions for the Production of Casualties Among Military Personnel in the Field.* Final Report for the United States—United Kingdom—Canadian Chemical Warfare Advisory Sub-Committee, by W. D. Walters, and others, July 20, 1944.

OPEN LITERATURE

3. Fries, A. A., and C. J. West. *Chemical Warfare*. McGraw-Hill, New York, 1921 (page 160).

Chapter 2

OSRD FORMAL REPORTS

1. OSRD 571. *Stability of Cyanogen Chloride. Constants for Various Charcoals with Cyanogen Chloride. Preparation of Cyanogen and Nitrogyl Chloride*, W. M. Latimer, University of California, April 14, 942.
2. OSRD 1432. *Hydrogen Cyanide Toxicity Studies*, by J. M. Coon, Howard Ghose, L. S. Sonnie and C. C. Lushbaugh, University of Chicago, May 18, 1943. Div. 9-323.2 M1
3. OSRD 5001. *Cyanogen Chloride: Improved Toxicity Studies*, by J. M. Coon, George J. Benoit, and Donald A. Van Haesen, University of Chicago, April 28 1945 Div. 9-323.1-M.4
4. OSRD 5467. *Stabilization of ClK*, by Max S. Kharasch, University of Chicago, August 21, 1945. Div. 9-223.1-M8

OSRD INFORMAL REPORTS

5. Contract NDCrc-113, University of Southern California, Anton B. Burg.
   a. Informal Report 10.38-25, July 15, 1943. Div. 9-223.3-M2
   b. Informal Report 10.38-30, August 15, 1943. Div. 9-223.3-M2
   c. Informal Report 10.4-34, September 15, 1943. Div. 9-223.3-M2
   d. Informal Report 10.4-37, October 14, 1943. Div. 9-223.3-M2
   e. Informal Report 10.4-39, November 15, 1943. Div. 9-223.3-M2
   f. Informal Report 10.4-44, December 14, 1943 Div. 9-223.3-M2
   g. Informal Report 10.4-47, January 15, 1944. Div. 9-223.1-M1
   h. Informal Report 10.4-50, February 14, 1944. Div. 9-223.1-M1
   i. Informal Report 10.4-52, March 13, 1944. Div. 9-223.1-M1
   j. Informal Report 10.4-58, April 15, 1944. Div. 9-223.1-M1
   k. Informal Report 10.4-61, May 15, 1944. Div. 9-223.3-M2
   l. Informal Report 10.4-66, June 15, 1944. Div. 9-223.1-M1
   m. Informal Report 10.4-68, July 15, 1944. Div. 9-223.1-M1
   n. Informal Report 10.4-70, August 15, 1944. Div. 9-223.1-M1

o. Informal Report 10.4-72, September 15, 1944. Div. 9-223.1-M1
p. Informal Report 10.4-76, October 14, 1944. Div. 9-223.1-M1
q. Informal Report 10.4-78, November 15, 1944. Div. 9-223.1-M1
r. Informal Report 10.4-79, December 14, 1944. Div. 9-22[illegible]
s. Informal Report 10.4-80, January 14, 194[illegible] Div[illegible]

6. Contract NDCrc-132, University of [illegible] Laboratory, E. M. K. Geiling, Inf. M[illegible] on *Toxicity of Chemical Warfare A[illegible]* [illegible]2
a. No. 4 May 10, 1943. [illegible]-M2
b. No. 10, May 10, 1944. [illegible]-M2
c. No. 17 June 10, 1944 [illegible]-123-M2
d. No. 18 July 10, 1944 [illegible] 9-123-M2
e. No. 19, August [illegible] Div. 9-123-M2
f. No. 20, Septem[illegible] Virginia, John H.
g. No. 21, Octo[illegible] [illegible]ed February
h. No. 22 Nov[illegible] Div. 9-415-M2

7. Contract OEM[illegible] [illegible]ersity of Chicago, Morgan, Lefevre, [illegible] 10, 1945. [illegible] on the *Stabilization of CK*, Div. 9-223.1-M3

8. Contract [illegible]
a. [illegible] Report on the *Stabilization of CK*, Div. 9-223.1-M3
b. [illegible] Report on the *Stabilization of CK*, Div. 9-223.1-M3
c. [illegible] Report on the *Stabilization of CK*, Div. 9-223.1-M3
d. [illegible] Report on the *Stabilization of CK*, Div. 9-223.1-M3
e. [illegible] Report on the *Stabilization of CK*, Div. 9-223.1-M3
f. [illegible] Report on the *Stabilization of CK*, 194[illegible] Div. 9-223.1-M3
[illegible] University of Chicago, E. S. [illegible], *Poisoning. A Preliminary Note*, Div. 9-323.1-M1

9

[illegible] STATES ARMY REPORTS

Chemical Warfare Service

[illegible] Division, American University Experiment [illegible], Washington, D. C., Pharmacological and Research Rept. No. 222. *Toxicity of Cyanogen [illegible] for the Dog, Rabbit, Guinea Pig, Cat, and Mouse*, tabulated by E. K. Marshall, Jr., and E. J. Miller,

IRD [illegible] "The Toxicity of Hydrogen Cyanide Acid Gas on [illegible], Mice, Guinea Pigs, and Rabbits." By C. A. Armstrong, A. R. Koontz, M. G. Witherspoon, assembled 31, 1923.

CATR [illegible] *Toxicity of Hydrocyanic Acid Gas to Mice by Inhalation for a 10-Min. Exposure*, by G. C. Armstrong, May [illegible], 1933.

13. F[illegible] *Cyanogen Chloride: II Toxicity: Median [illegible] for Mice*, February 1941.
14 [illegible] *Median Lethal Concentrations for Mice: 2-[illegible]*, by S. D. Silver, R. L. Ferguson, [illegible] C. M. Hunt, November 26, 1941.
[illegible] *Hydrocyanic Acid. The Toxicity and Speed [illegible] Man*, November 17, 1942.
[illegible] No. 8. *Stability of CC in Thin-walled Chemical [illegible]*, by T. S. Matter, 2nd Lt., CWS, October 6, 1943.
DPGMR No. 10. *Stability of Various Grades of CC in Chemical Bombs After 30, 60, and 90 Days at 65° C.*, by T. S. Matter, 2nd Lt., CWS, 1943.
19. DPGMR No. 16. *Third Progress Report on Surveillance Tests of Cyanogen Chloride*, by Thurston D. Brown, Captain CWS, April 27, 1944.
20. DPGMR No. 17. *AC Surveillance*, by A. B. Isenburger and L. I. Swearingen, June 1, 1944.
21. Dugway Proving Ground, Weekly Reports
a. For the period ending January 30, 1945 (Rep. No. 93).
b. For the period ending March 20, 1945 (Rep. No. 100).
c. For the period ending April 10, 1945 (Rep. No. 103).
d. For the period ending April 24, 1945 (Rep. No. 105).
e. For the period ending May 1, 1945 (Rep. No. 106).
22. Chemical Warfare Service, Research and Development Program, Dugway Proving Ground. Report for month of August 1945.
23. TRLR 22. *Hydrocyanic Acid. LC_{50} for Rats Exposed 2 Minutes*, January 1944.
24. TRLR 23. *Hydrocyanic Acid. LC_{50} for Goats: 2 Min. Exposure: Time for Incapacitation*, January 7, 1944.
25. TRLR 26. *Cyanogen Chloride. LC_{50} for Goats, 2 Min. Exposure*, March 28, 1944.
26. Medical Division Rep. No. 19, *Oral Toxicity of Cyanogen Chloride in Water to Rats*, January 6, 1945.
27. Medical Division, Edgewood Arsenal, Report No. 26, *Intravenous Toxicity Studies of Cyanogen Chloride and Sodium Cyanide in Dogs, Goats, and Rabbits*, March 10, 1945.
28. Medical Division Report No. 34. *The Pathology of CK on Inhalation*, June 19, 1945.
29. Medical Division Report No. 39. *Residual Lesions of the Central Nervous System in Cyanide Poisoned Animals*, July 12, 1945.
30. Medical Division Status Summaries, published as AC'S Field Laboratory Memo 1-4-5, Edgewood Arsenal, August 1944.
31. Medical Research Laboratory (Dugway Proving Ground) Report No. 3, *A Study of Short Interval Exposures of Goats to CG, CK, and AC*, November 28, 1945.
32. Medical Division, Edgewood Arsenal.
a. Inf. Monthly Prog. Rept. April 15, 1945.
b. Inf. Monthly Prog. Rept. Sept. 15, 1945.
c. Inf. Monthly Prog. Rept. Oct. 15, 1945.
33. MRL, Edgewood Arsenal.
a. Inf. Monthly Prog. Rept. April 15, 1944.
b. Inf. Monthly Prog. Rept. June 15, 1944.

34. TRL, Edgewood Arsenal.
a. Inf. Monthly Prog. Rept. No. 3, July 15, 1944
b. Inf. Monthly Prog. Rept. No. 4, Aug. 15, 1944.
35. C.W.S. Specifications 106-21-16B, October 20, 1942.
36. U. S. Army Specifications 96-81-219, August 4, 1945.
37. U. S. Army Specifications No. 96-21-32A, August 25, 1945.
38. Contract W-18-035-CWS-883, The University of Southern California, A. B. Burg.
a. *Stabilization of Cyanogen Chloride XXI*, April 1, 1945.
b. *Stabilization of Cyanogen Chloride XXII*, May 1, 1945.
c. *Stabilization of Cyanogen Chloride XXIII*, June 1, 1945.
d. *Stabilization of Cyanogen Chloride XXIV*, July 1, 1945.
e. *Stabilization of Cyanogen Chloride XXV*, August 1, 1945.
f. *Stabilization of Cyanogen Chloride XXVI*, Sept. 1, 1945.
39. Contract W-40-037-CWS-23, University of Chicago Toxicity Laboratory.
a. April 15, 1945.
b. May 15, 1945.
c. June 15, 1945.
d. October 15, 1945.

UNITED STATES ARMY

40. *The Toxicity of AC, CK, and CG*, by Capt. J. O. Hutchens, Toxicological Research Laboratory, Medical Division, CWS, and Dr. M. A. Lipton, NDRC, University of Chicago Toxicity Laboratory, December 1944.

UNITED STATES—UNITED KINGDOM REPORTS

41. PCS Rept. No. 1. *Status Summary on the Relative Values of AC, CK and CG as Bomb Fillings*, by Project Coordination Staff, July 10, 1944.
42. PCS Rept. No. 2. *Status Summary on the Protection Against Non-Persistent Agents by Allied and Enemy Canisters Under Tropical Conditions*, by Project Coordination Staff, July 19, 1944.
43. PCS Rept. No. 9. *Résumé of Recent Knowledge on the Technical Aspects of Chemical Warfare in the Field*, by Project Coordination Staff, May 17, 1945.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

44. Porton Report No. 2003. *The Effects of CC on Experimental Animals and Human Subjects*, March 10, 1944.
45. Porton Report No. 2661. *The Action and Fate of CC in the Body*, November 24, 1944.
46. Porton Report No. 2688. *The Mechanism of CK Poisoning*, May 30, 1945.
47. Porton Report No. 4221 (V. 6240). *Interim Report on the Storage and Stability of CC*, May 20, 1944.

CANADIAN REPORTS

Experimental Station, Suffield, Alberta

48. Suffield Technical Minute No. 41. *The Stability of Cyanogen Chloride*, by F. A. Hochstein, November 18, 1943.
49. Suffield Technical Minute No. 93. *Observations of the Skin Sensations Experienced During Exposure to CK*, April 20, 1945.

Extramurai Research

50. C. E. 165, 111-1-1231, October 15, 1943, *The Vapor Pressures of the System Hydrogen Cyanide—Cyanogen Chloride*, by A. K. Archibald, C. C. Coffin, and T. R. Ingraham, Dalhousie University.

OPEN LITERATURE

51. Chattaway, F. D., and J. Mello Wadmore. *The Constitution of Hydrocyanic, Cyanic and Cyanimic Acids*. J. Chem. Soc. **81**, 191–203 (1902).
52. Gettler, A. O., and J. O. Baine. *The Toxicology of Cyanide*. Am. J. Med. Sci. **196**, 189 (1938).
53. Holstrøm, F., and K. O. Møller. *The Content of Cyanide in Human Organs from Cases of Poisoning with Cyanide Taken by Mouth. With a Contribution to the Toxicology of Cyanides*. Acta pharmacol. et toxicol. **1**, 1–17 (1945).
54. Jennings, W. J., and W. B. Scott. *The Preparation of Cyanogen Chloride*. J. Am. Chem. Soc. **41**, 1241–1248 (1919).
55. Loevenhart, A. S., J. Y. Malone, and A. G. Martin. *The Action of Respiratory Stimulants Upon the Respiration When Depressed by Increased Intracranial Pressure With Special Reference to Sodium Cyanide*. J. Pharm. and Ex. Therap. **19**, 13 (1922).
56. Loevenhart, A. S., W. F. Lorenz, A. G. Martin, and J. Y. Malone. *Stimulation of the Respiration by Sodium Cyanide and Its Clinical Application*. Arch. Int. Med. **21**, 109 (1918).
57. Robb, G. R., and Soma Weiss. *A Method for the Measurement of the Velocity of the Pulmonary and Peripheral Venous Blood Flow in Man*. Am. Heart J. **8**, 650 (1932–33).
58. Wurtz, A. *Beobachtungen über einige Cyanverbindungen*. Ann. **64**, 307–308 (1847).
59. Wurtz, A., *Mémoire sur les combinaisons du cyanogène*. Compt. Rend. **24**, 436–439 (1847).

Chapter 3

OSRD FORMAL REPORTS

1 OSRD 332. *The Catalytic Conversion of Diphosgene into Phosgene*, by M. S. Kharasch, University of Chicago, January 9, 1942. Div 9-221.31-M1
2. OSRD 504. *The Preparation of Diphosgene*, by M. S. Kharasch, University of Chicago, April 15, 1942. Div. 9-231.31-M2
3. OSRD 734. *Diphosgene: Median Lethal Concentrations for Mice for a Ten Minute Exposure*, by Morris A. Lipton,

George J. Rotariu, and Clarence C. Lushbaugh, University of Chicago Toxicity Laboratory, July 20, 1942.
Div. 9-331.1-M1

4. OSRD 899. *Catalytic Conversion of Diphosgene to Phosgene Within Closed Heavy Metal Containers*, by M. S. Kharasch, University of Chicago, September 28, 1942.
Div. 9-231.31-M3

5. OSRD 1036. *I. Rapid Methods for Synthesizing Certain War Gases. II. The Chemistry of the Sulfur Fluorides*, by J. H. Simons, Pennsylvania State College, October 21, 1942. Div. 9-200-M3

6. OSRD 1106. *Preliminary Tube Tests With ClCF*, by R. G. Dickinson, California Institute of Technology, December 8, 1942. Div. 9-231.33-M1

7. OSRD 1437. *Preparation of Diphosgene*, by S. Temple, E. I. du Pont de Nemours and Company, May 20, 1943.
Div. 9-231.31-M4

8. OSRD 1806. *Toxicity Studies of Carbonyl Chlorofluoride*, by Julius M. Coon, Lawrence S. Sonkin, Clarence C. Lushbaugh, and George J. Rotariu, University of Chicago Toxicity Laboratory, September 13, 1943.
Div. 9-331.2-M1

9. OSRD 4637. *Phosgene: Special Studies*, by Julius M. Coon, George S. Rotariu, Clarence C. Lushbaugh, and Drucilla Van Hoesen, University of Chicago Toxicity Laboratory, January 27, 1945. Div. 9-331.1-M9

OSRD INFORMAL REPORTS

10. Contract NDCrc-132, University of Chicago Toxicity Laboratory, E. M. K. Geiling. Inf. Month. Prog. Rept. NDRC 9:4:1 No. 6, July 10, 1943. Div. 9-125-M2

11. Contract NDCrc-136, Harvard University, Paul D. Bartlett, Inf. Month. Prog. Rept., February 10, 1944.
Div. 9-235-M11

12. Contract OEMemr-13, University of Pennsylvania, J. S. Lockwood.
    a. Progress Report No. 14, February 1, 1944.
    Div. 9-331.1-M5
    b. *The Effects in Rats and Dogs of Preliminary Deprivation of Water or Food on Survival from Phosgene Poisoning*, May 11, 1944. Div. 9-331.1-M9
    c. Report of June, 1944. Div. 9-331.1-M8

13. Contract OEMemr-57, University of Chicago, E. S. G. Barron. *Diphosgene Poisoning*, December 20, 1943.
Div. 9-331.1-M4

14. Contract OEMemr-114, University of Chicago, R. W. Gerard.
    a. Report No. 7. *Final Report on the Role of Acid in Diphosgene Action: A Note on Ketene*, February 12, 1943. Div. 9-331.1-M2
    b. Report No. 11. *Pitressin and Dehydration in the Treatment of Diphosgene Poisoning*, January 12, 1944. Div. 9-324-M2
    c. Report No. 12. *Interim Report on Diphosgene (and Phosgene)*, February 26, 1944. Div. 9-331.1-M6

MISCELLANEOUS

15. *Fascicles on Chemical Warfare Medicine*, prepared for Committee on Medical Research of the Office of Scientific Research and Development by the Committee on Treatment of Gas Casualties, Division of Medical Sciences of the National Research Council, Washington, D. C., 1945.
Div. 9-110-M1
Div. 9-110-M2
Div. 9-110-M3

16. Informal Report on *The Physiological Action of Phosgene*, by S. Ruben with the assistance of A. A. Benson and C. N. Rice. Report written and made available to NDRC by T. H. Norris, University of California, October 22, 1943.
Div. 9-331.1-M3

UNITED STATES ARMY REPORTS

17. Research Division, American University Experiment Station, Washington, D. C. Pharmacological and Research Section, Reports 301-330, 1918.

18. EAMRD 15. *Minimum Lethal Concentrations, Symptomatology, and Pathology of Phosgene*, September 1923.

19. EAMRD 40. *The Actual Lethal Dose of Phosgene*, May 31, 1925.

20. EATR 110. *Toxicity of Phosgene to White Mice by Inhalation*, March 1933.

21. EATR 270. *The Detection of Phosgene by Odor*, March 31, 1938.

22. EATR 354. *Phosgene: Median Lethal Concentration for Mice: 2- and 30-Minute Exposures*, 1941.

23. Contract W-49-036-CWS-1, New York University College of Medicine, *Phosgene: Review of the Literature on the Effect of Exposure in Man and Experimental Animals*, by Herbert Chasis, November 1, 1943.

24. *Medical Division Status Summaries*, published as CWS Field Laboratory Memo 1-4-5, Edgewood Arsenal, August 1944.

25. War Department Technical Manual 8-285, *Treatment of Casualties from Chemical Agents*, April 1945.

26. Medical Division, Report No. 49. *A Study of the Residual Effects of Phosgene Poisoning in Human Subjects*, August 24, 1945.

27. Medical Research Laboratory (Dugway Proving Ground) Report No. 3. *A Study of Short Interval Exposures of Goats to CG, CK, and AC*, November 28, 1945.

28. TRLR 20. *Phosgene: LD_{50} for Goats: 2 min. Exposure*. December 15, 1943.

OSRD REPORTS

UNITED STATES ARMY

29. *The Toxicity of AC, CC, and CG*, by J. O. Hutchens, Edgewood Arsenal, and M. A. Lipton, University of Chicago (Contract NDCrc-132), December 1944.

UNITED STATES—UNITED KINGDOM REPORTS

30. Project Coordination Staff (Edgewood Arsenal) PCS Rept. No. 1. *Status Summary on the Relative Values of AC, CK, and CG as Bomb Fillings*, July 10, 1944.

31. PCS Rept. No. 9. *Résumé of Recent Knowledge on the Technical Aspects of Chemical Warfare in the Field*, May 17, 1945.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

32. Porton Report 2316. *The Effect of Phosgene at Low Concentrations for Long Periods*, October 12, 1941.
33. Porton Report 2349. *The Effect of Previous Dehydration on the Mortality From Phosgene, in First Report on Phosgene Poisoning* (W. 2494 and W. 4700), April 1942.
34. Porton Report 2555. *Phosgene Poisoning in the Horse and Mule*, November 2, 1943.
35. Ptn. 2989 (A. 7091). *The Variation in $LC(t)_{50}$ of Phosgene For Small Animals with Duration of Exposure*, September 12, 1945.

CANADIAN REPORTS

Chemical Warfare Laboratories, Ottawa

36. Development Section Report No. 109. *Preparation of Diphosgene by the Light-activated Chlorination of Methyl Formate*, by A. K. Ames and C. H. R. Thompson, June 25, 1945.

National Research Council of Canada

37. N.R.C. Report SR7 643, Excerpt from *Preparation of Carbonyl Fluoride*. (British Report V. 13089).

Extramural Research

38. University of New Brunswick (R. H. Wright) (C.E. 169).
    a. *The Preparation of Diphosgene*, by H. M. Macfarlane, F. J. Toole, and R. H. Wright, April 1, 1944.
    b. *Experiments on the Decomposition of Diphosgene and the Instantaneous Production of Phosgene Clouds*, by H. M. Macfarlane, F. J. Toole, and R. H. Wright, July 21, 1944.
39. University of Toronto (C. C. Lucas) (C. E. -11) Report C. P. 15, *Experimental Phosgene Poisoning (Rhesus Monkeys)*, by C. C. Lucas and E. Semmens, February 1942.

OPEN LITERATURE

40. Grignard, V., G. Rivate and Ed. Urbain, *Recherches sur la chloruration du formiate et du chloroformiate de méthyle*, Compt. Rendu **169**, 1074-1077 (1919).
41. Grignard, V., G. Rivate and Ed. Urbain, *Sur les dérivés chlorés du formiate et du carbonate de méthyle*, Compt. Rendu **169**, 1143-1147 (1919).
42. Rentschel, W., *Über perchlorte Ameisensäureemethylather und verwandte Körper*, J. prakt. Chem. **36**, 99-113 (1887).
43. Haul, H. P., and H. Murdoch, *Superpalite*, J. Phys. Chem. **23**, 498-512 (1919).
44. Kling, A., D. Florentin, A. Lassieur and R. Schmutz, *Préparation des chloroformiates de méthyles chlorés*, Compt. Rend. **169**, 1046-1047 (1919).
45. Prentiss, A. M., *Chemicals in War*, McGraw-Hill, New York, 1937.
46. Sartori, Mario, *The War Gases*, New York, D. van Nostrand Company, Inc. (1939).
47. Winternitz, M. C., *Pathology of War Gas Poisoning*, Yale University Press, 1920.

Chapter 4

OSRD FORMAL REPORTS

1. OSRD 179. *Improved Methods of Preparation and Preliminary Study of Physical and Chemical Properties of Compound 1130*, by A. B. Burg, University of Southern California, November 13, 1941. Div. 9-212.2-M1
2. OSRD 294. *The Preparation and Properties of 1130 — II*, by A. B. Burg, University of Southern California, December 30, 1941. Div. 9-212.2-M2
3. OSRD 300. *Preliminary Examination of 1130 Removal*, by Roscoe G. Dickinson, California Institute of Technology, December 18, 1941. Div. 9-364-M1
4. OSRD 437. *The Value of Soda Lime in Gas Absorbents*, by W. C. Pierce, E. O. Wiig, P. A. Leighton, R. G. Dickinson, W. M. Latimer, M. Dole, and W. A. Noyes, Jr., March 6, 1942. Div. 9-350-M1
5. OSRD 616. *Comparative Retentivities of Whetlerite and Type D Mixture for SeF_4 and for 1130*, by Roscoe G. Dickinson, California Institute of Technology, May 9, 1942. Div. 9-350-M2
6. OSRD 770. *Heat of Formation of S_2F_{10}*, by Hugh M. Huffman, California Institute of Technology, July 29, 1942. Div. 9-212.2-M3
7. OSRD 879. *The Chemical Detection of 1130*, by D. S. Tarbell, University of Rochester, September 11, 1942. Div. 9-422.121.1-M3
8. OSRD 934. *Calorimetric Studies II, The Entropy and Free Energy of S_2F_{10}*, by Hugh M. Huffman, California Institute of Technology, October 10, 1942. Div. 9-212.2-M4
9. OSRD 1036. *I. Rapid Methods for Synthesizing Certain War Gases. II. The Chemistry of the Sulfur Fluorides*, by J. H. Simons, The Pennsylvania State College, October 21, 1942. Div. 9-200-M3
10. OSRD 1053. *Thermodynamic Data on S_2F_{10}*, by Hugh M. Huffman, California Institute of Technology, November 21, 1942. Div. 9-212.2-M5
11. OSRD 3030. *Toxicity, Pathological, and Choreal-Penetration Studies of Sulfur Pentafluoride*, by Julius M. Cuon, Clarence C. Lushbaugh, Morris A. Lipton, and Lawrence S. Sonkin, University of Chicago Toxicity Laboratory, December 30, 1943. Div. 9-312.2-M1
12. OSRD 4012. *The Preparation of New Toxic Gases*, by A. B. Burg, University of Southern California, August 12, 1944. Div. 9-212.2-M8
13. OSRD 4176. *Status Report of Toxicity and Vesicant Tests of Compounds Referred to the University of Chicago Toxicity Laboratory*, by Hoylande D. Young, October 3, 1944. Div. 9-300-M4
14. OSRD 4637. *Phosgene: Special Studies*, by Julius M. Cuon, George J. Rotariu, Clarence C. Lushbaugh, Drusilla Van Hoesen, University of Chicago Toxicity Laboratory, January 27, 1945. Div. 9-331.1-M9
15. OSRD 5146. *Final Report under Contract OEMsr-532*, by Barnett Cohen, Joseph Harris, E. R. Van Artsdalen, and Marie E. Perkins, Johns Hopkins University, May 29, 1945. Div. 9-200-M10

Chapter 5

In addition to the references cited in the text, the following bibliography on H and analogs includes for completeness a number of related reports on the chemical, physical, and toxicological properties of members of the sulfur mustard series.

OSRD FORMAL REPORTS

1. OSRD 78. *Report on "T" Glycol*, by Roger Adams and C. S. Marvel, University of Illinois, March 17, 1941. Div. 9-212.111-M1
2. OSRD 276. *The Toxicity of β-Chloroethylthiocholine-chloride*, by E. M. K. Geiling and F. C. McLean, University of Chicago Toxicity Laboratory, December 13, 1941. Div. 9-331.3-M1
3. OSRD 314. *Preparation of Organometallic Compounds as Sources of Toxic Oxide Smokes and Flame Thrower Fuels*, by Henry Gilman, Iowa State College, January 9, 1942. Div. 9-210-M1
4. OSRD 527. *The Toxicity of Mustard (Redistilled Levinstein)* by Julius M. Coon, Jules H. Last, Clarence C. Lushbaugh, and George J. Rotariu, University of Chicago Toxicity Laboratory, April 24, 1942. Div. 9-312.1-M1
5. OSRD 548. *Organo-Tin Compounds*, by Henry Gilman, Iowa State College, May 2, 1942. Div. 9-216-M1
6. OSRD 593. *bis(2-Chloroethyl) sulfone: Toxicity Upon Inhalation and Vesicant Properties*, by Morris A. Lipton, George J. Rotariu, Clarence C. Lushbaugh, and Jules H. Last, University of Chicago Toxicity Laboratory, May 28, 1942. Div. 9-312.3-M1
7. OSRD 693. *A Method for Delivering Equal Amounts of Fluids of Differing Physical Properties*, by P. D. McMaster, Rockefeller Institute for Medical Research, July 10, 1942. Div. 9-371-M2
8. OSRD 840. *The Preparation of Mustard Gas and Certain of its Derivatives and Analogs*, by C. S. Marvel and R. C. Fuson, University of Illinois, August 31, 1942. Div. 9-212.11-M2
9. OSRD 846. *Preparation of Cadmium Salts and Organocadmium Compounds*, by Henry Gilman, Iowa State College, August 26, 1942. Div. 9-215-M1
10. OSRD 855. *The Corrosion of Metals by Mustard Gas*, by C. S. Marvel and R. C. Fuson, University of Illinois, August 26, 1942. Div. 9-254-M3
11. OSRD 878. *Summary Report on Work Done on Chemical Warfare Problems at the University of Illinois*, by C. S. Marvel and R. C. Fuson, University of Illinois, September 11, 1942. Div. 9-200-M2
12. OSRD 933. *The By-Products of Commercial Mustard Gas Made From Ethylene and the Sulfur Chlorides*, by Marvin Carmack and Richard Handrick, University of Pennsylvania, October 8, 1942. Div. 9-212.11-M3
13. OSRD 1016. *Freezing Points of Binary HS Mixtures*, by P. D. Bartlett, Harvard University, November 9, 1942. Div. 9-212.112-M4
14. OSRD 1111. *Preparation of B.L.*, by Chemical Department, E. I. du Pont de Nemours and Company, December 8, 1942. Div. 9-513.1-M1
15. OSRD 1221. *Experimental Manufacture and Process Study of BAL*, by Jackson Laboratory, E. I. du Pont de Nemours and Company, December 8, 1942. Div. 9-513.1-M2
16. OSRD 1284. *Possible Toxic Agents and Intermediates*, by M. S. Kharasch, University of Chicago, March 22, 1943. Div. 9-200-M5
17. OSRD 1377. *A Survey of Sulfur Compounds that Have Been Studied for Vesicant Activity*, by R. C. Fuson, C. S. Marvel, and C. C. Price, University of Illinois, April 30, 1943. Div. 9-212.5-M1
18. OSRD 1391. *Toxic Effects of Compounds Related to Mustard 1. Toxic Effects of Mustard, Mustard Sulfone, Sesqui-Mustard, and Sesqui-Mustard Analogues*, by Morris A. Lipton, Simon Black, James E. Lavalle, and C. C. Lushbaugh, University of Chicago Toxicity Laboratory, May 7, 1943. Div. 9-312.1-M2
19. OSRD 1504. *Thallium Compounds*, by Henry Gilman, Iowa State College, June 9, 1943. Div. 9-217-M1
20. OSRD 1517. *Organo Lead Compounds as Sternutators*, by Henry Gilman, Iowa State College, June 16, 1943. Div. 9-218-M1
21. OSRD 1978. *Composition of Levinstein Mustard*, by Charles L. Thomas, Universal Oil Products Company, October 20, 1943. Div. 11-203.511-M2
22. OSRD 2003. *Purification of Levinstein Mustard by Crystal Fractionation*, by Louis S. Kassel and Curtis F. Gerald, Universal Oil Products Company, November 9, 1943. Div. 11-203.511-M3
23. OSRD 3084. *Selenonium and Sulfonium Halides*, by C. D. Hurd, Northwestern University, January 1, 1944. Div. 9-219-M3
24. OSRD 3179. *Storage Characteristics and Stabilization of Levinstein H*, by J. C. Woulhouse, A. S. Weygandt, M. T. Grebel, E. R. Beller, A. D. Johnson, H. B. Fernald, and C. L. Robinson, Gnosselli Chemical Department, E. I. du Pont de Nemours and Company, January 19, 1944. Div. 9-212.112-M9
25. OSRD 3217. *Purification of Levinstein Mustard*, by W. E. Kuhn, G. B. Arnold, and L. E. Ruddick, The Texas Company, February 5, 1944. Div. 11-203.511-M5
26. OSRD 3551. *Preparation and Stability of the Nitrogen Mustards*, by George H. Coleman, Joseph E. Callen, Chester M. McCloskey, Gust Nichols, Ronald E. Pyle, Robert L. Sundberg, and Frank A. Stuart, The State University of Iowa, April 27, 1944. Div. 9-221.1-M10
27. OSRD 3558. *Mustard Gas from Thiodiglycol and Thionyl Chloride*, by R. Norris Shreve, David Austin Frost, and Lewis Ambrose McDonald, Purdue Research Foundation, May 1, 1944. Div. 9-212.111-M2
28. OSRD 3621. *Treatment of Water Contaminated by Chemical Warfare Agents*, by A. M. Buswell, C. C. Price, A. C. Wiese, H. E. Hudson, and R. C. Gore, University of Illinois, May 13, 1944. Div. 9-501-M4
29. OSRD 3929. *The Preparation of Ethanedithiol*, by H. W. Eley, C. B. Buswell, and Alvan Doman, E. I. du Pont de Nemours and Company, August 1, 1944. Div. 9-212.113-M1
30. OSRD 3944. *A Vapor-Train Study of the Comparative Vesicancy of Mustard and Several Related Amines and Sulfides on Human Skin*, by Simon Black, Kenneth P

Du Bois and Morris A. Lipton, University of Chicago Toxicity Laboratory, August 30, 1944.
Div. 9-361.1-M1

31. OSRD 3959. *An Investigation of Heated Mustard Gas*, by R. C. Fuson, University of Illinois, July 28, 1944.
Div. 9-212.11-M7

32. OSRD 3964. *The Behavior of Hexamine in Levinstein Mustard*, by R. C. Fuson, University of Illinois, July 28, 1944.
Div. 9-212.112-M10

33. OSRD 4008. *The gamma-Fluorobutyrates and Related Toxic Compounds*, by Morris S. Kharasch, University of Chicago, August 11, 1944.
Div. 9-231.32-M3

34. OSRD 4176. *Status Report on Toxicity and Vesicant Tests of Compounds Referred to the University of Chicago Toxicity Laboratory, Through July, 1944*, by Hoylande D. Young, University of Chicago, University of Chicago Toxicity Laboratory, October 3, 1944.
Div. 9-300-M4

35. OSRD 4177. *The Composition of Levinstein Mustard*, by R. C. Fuson, C. C. Price, R. A. Bowman, N. E. Foster, and R. P. Lipscomb, University of Illinois, September 26, 1944.
Div. 9-212.112-M11

36. OSRD 4195. *The Synthesis of Certain Mustard Analogs*, by C. R. Noller and L. Kaplan, Stanford University, September 27, 1944.
Div. 9-212.11-M8

37. OSRD 4230. *The Beurah Micropipette*, by William Bloom, John F. Thomson, Eugene Goldwasser, Joseph Savit, and Peter De Bruyn, University of Chicago Toxicity Laboratory, October 9, 1944.
Div. 9-371-M4

38. OSRD 4273. *A Summary of the Vapor Pressures and Volatilities of Compounds Studied at the University of Chicago Toxicity Laboratory up to August 1, 1944*, by C. Ernst Redemann *et al.*, University of Chicago Toxicity Laboratory, November 4, 1944.
Div. 9-200-M8

39. OSRD 4303. *The Preparation and Stability of Nitrogen Mustards and Related Compounds*, by George H. Coleman, Joseph E. Cullen, Clinton A. Dornfeld, Chester M. McCloskey, Gust Nichols, Robert L. Sandberg, The State University of Iowa, November 2, 1944.
Div. 9-221.1-M15

40. OSRD 4304. *A Continuous Process for the Preparation of Mustard and Sesqui-Mustard*, by R. C. Fuson, C. C. Price, R. E. Foster, P. D. Lipscomb, H. R. Snyder, University of Illinois, October 31, 1944.
Div. 9-212.11-M10

41. OSRD 4308. *The Structure of Propyl Mustard and Its Analogs*, by C. C. Price, H. R. Snyder, D. M. Burness, and R. C. Fuson, University of Illinois, November 2, 1944.
Div. 9-212.112-M12

42. OSRD 4331. *2-Chloroethyl 2,2-Dichloroethyl Sulfide (2-Chloro-H)*, by R. C. Fuson, C. C. Price, H. R. Snyder, and W. E. Parham, University of Illinois, January 1, 1945.
Div. 9-212.112-M13

43. OSRD 4532. *Synthesis and Characterization of 2-Chloroethyl 2-Hydroxyethyl Sulfide (ClH)*, by R. C. Fuson, C. C. Price, H. R. Snyder, E. N. Marvell, and J. B. Ziegler, University of Illinois, January 1, 1945.
Div. 9-212.114-M1

44. OSRD 4533. *Organic Arsenicals and Other Toxic Agents*, by C. S. Hamilton, E. J. Crayon, Jr., H. J. Andres, R. F. Coles, and Bill Ehlers, University of Nebraska, January 1, 1945.
Div. 9-219-M4

45. OSRD 4585. *A New Chamber for the Determination of Toxicities by Total Body or Head Exposure*, by John O. Hutchens, H. W. Gurney, Robert S. Merrill, Howard G. Glaus, Harry C. Allaum, and James H. M. Henderson, University of Chicago Toxicity Laboratory, January 17, 1945.
Div. 9-372-M5

46. OSRD 4834. *The Chemistry of Sulfonium Salts Related to H*, by Max Bergmann, Joseph S. Fruton, Calvin Columbic, Mark A. Stahmann, and William H. Stein, The Rockefeller Institute for Medical Research, March 19, 1945.
Div. 9-212.3-M2

47. OSRD 4835. *An Investigation of the Structure of the Lower Polysulfides*, by R. C. Fuson, C. C. Price, H. R. Snyder, Edgar Howard, Jr., and Sidney Melamed, University of Illinois, March 19, 1945.
Div. 9-212.12-M1

48. OSRD 4852. *I. The Necrotizing Action of Certain Substances Related to Mustard Gas, H, or to the Nitrogen Mustards. II. A Comparison of the Vesicant Action Exerted by Mustard Gas H, and by Mixtures of H with Wetting Agents or Solvents*, by George H. Hogeboom, Philip D. McMaster, Marion B. Sulzberger, Rudolf L. Baer, and Abram Kanof, March 25, 1945.
Div. 9-361.1-M3

49. OSRD 4999. *The Concentration of the Odorous Principle of Water-Washed Levinstein Mustard. The Preparation of 2-Chloroethyl Sulfenyl Chloride*, by C. C. Price and O. H. Bullitt, Jr., University of Illinois, April 26, 1945.
Div. 9-212.112-M14

50. OSRD 5000. *The Effect of Flow Rate on the Toxicities of H, Q, HN1, HN3 and L by Inhalation, by Total Exposure, and by Body Exposure*, by Harry C. Allaum, Dora Benedict Kenneth P. Du Bois, Howard S. Glaus, James H. M. Henderson, and John O. Hutchens, University of Chicago Toxicity Laboratory, April 28, 1945.
Div. 9-300-M1

51. OSRD 5030. *Some Aspects of the Chemistry of T as a Water Contaminant*, by Charles C. Price and Albert Pohland, The University of Illinois, May 2, 1945.
Div. 9-212.3-M3

52. OSRD 5032. *A Formal Analysis of the Action of Liquid Vesicants on Bare Skin*, by Herbert D. Landahl, University of Chicago Toxicity Laboratory, May 5, 1945.
Div. 9-300-M1

53. OSRD 5148. *Studies in the Synthesis of Organic Compounds of Sulfur, Nitrogen and Chlorine Which Possess Physiological Activity*, by R. C. Fuson, C. C. Price, and H. R. Snyder, University of Illinois, May 20, 1945.
Div. 9-212.5-M4

54. OSRD 5194. *Tests for Vesicancy on Human Skin*, by William Bloom, *et al.*, University of Chicago Toxicity Laboratory, June 1, 1945.
Div. 9-300-M3

55. OSRD 5281. *Organic Compounds Containing Fluorine*, by M. S. Kharasch, University of Chicago, June 28, 1945.
Div. 9-232-M7

56. OSRD 5305. *Supplement to OSRD 4176, Status Report on Toxicity and Vesicant Tests of Compounds Referred to the University of Chicago Toxicity Laboratory*, by R. K. Cannan, *et al.*, University of Chicago Toxicity Laboratory, July 4, 1945.
Div. 9-300-M5

82. Medical Division Report No. 11. *Sesquimustard (Q): LC_{50} to White Mice — 10 Minute Exposure*, June 30, 1945.
83. Medical Division Informal Monthly Progress Reports.
    a. December 15, 1944.
    b. September 15, 1945.
84. MIT-MR No. 41. *Stabilization of Levinstein H*, October 7, 1943.
85. MIT-MR No. 54. *A Study of the Impurities in Levinstein Mustard and Purified Levinstein Mustard*, February 18, 1944.
86. MIT-MR No. 66. *Purification of Levinstein H*, Part I: May 13, 1944. Part II: June 13, 1944.
87. MIT-MR No. 69. *The Cause and Prevention of the Separation of NDR-459 from Certain Freshly Thickened Levinstein H Solutions*, May 13, 1944.
88. MIT-MR No. 74. *Investigation of the Continuous Manufacture of Mustard Gas by the Sulfur Chloride Process*, June 20, 1944.
89. MIT-MR No. 101. *Storage Stability of Polymethylmethacrylate-thickened H*, September 28, 1944.
90. MIT-MR No. 117. *Agents for Preventing the Separation of Poly (Methyl Methacrylate) from Thickened Levinstein H*, January 5, 1945.
91. MIT-MR No. 121. *Polarographic Analysis of H and Impurities*, January 5, 1945.
92. MRL(EA) Report No. 9. *Continued Exposure of Human Eyes to H Vapor (MIT Subjects)*, January 1, 1944.
93. MRL(EA) Report No. 18. *Eye Examination of Factory Workers Handling H, CN, and CG*, April 19, 1944.
94. MRL(EA) Report No. 23. *Correlation of Eye Changes in Rabbits with CT Exposure to H*, June 12, 1944.
95. TDMR 194. *Toxic Dust. Preparation of bis(2-Chloroethylthio)ethane, Sesqui HS*, October 25, 1939.
96. TDMR 356. *New Compounds. Physical Constants of Certain Organic Compounds (Mustard Homologues)*, June 20, 1942.
97. TDMR 366. *Solutions of Sesqui-HS and HS-Sulfone for Use as Airplane Spray Agents*, April 30, 1942.
98. TDMR 374. *Median Lethal Concentration for Mice of a Mixture of 50% Mustard and 50% Lewisite*, May 16, 1942.
99. TDMR 390. *Toxic Dust. The Large-Scale Laboratory Preparation of HS Sulfone*, June 22, 1942.
100. TDMR 423. *Methods of Analysis and Detection of Chemical Agents. The Composition of Plant Levinstein HS*, August 30, 1942.
101. TDMR 436. *Data on Chemical Warfare*, November 25, 1942.
102. TDMR 457. *A Mixture of 50% Lewisite, 50% Mustard. The Median Lethal Dosage by Skin Application*, October 20, 1942.
103. TDMR 470. *2-Chloro-1, 3-bis(2-Chloroethyl Sulfide)propane: Vesicant Action and Pain-producing Effect*, November 11, 1942.
104. TDMR 487. *Simulated HS and Simulated Thickened HS*, December 9, 1942.
105. TDMR 524. *bis(3-Chloroethylthioethyl) ether (T) and Its Mixtures with Mustard (HT)*, January 18, 1943.
106. TDMR 526. *Tert-butyl 2-Chloroethyl Sulfide and Tert-butyl Chloroethiolacetate*, January 8, 1943.
107. TDMR 564. *Comparative Vesicant Action and Cloth Penetration of Mixtures of Various Compounds with Mustard and Lewisite*, February 19, 1943.
108. TDMR 575. *HQ and HT. Review of British and United States Literature*, February 18, 1943.
109. TDMR 582. *Sesquimustard and Sesquimustard Homologues. Vesicant Action and Cloth Penetration of Undiluted Compounds and Mixtures with Mustard and Lewisite*, March 15, 1943.
110. TDMR 602. *Stabilization of Levinstein HS in Storage. A Conductivity Method for Evaluation of Stabilizers for Levinstein HS*, March 27, 1943.
111. TDMR 612. *Levinstein Mustard: Composition, Purification, Stabilization*, April 15, 1943.
112. TDMR 615. *Median Detectable Concentrations by Odor of Plant Run Mustard, Plant Run Lewisite, and Pilot Plant Ethyl Nitrogen Mustard*, April 16, 1943.
113. TDMR 618. *Tertiary Butyl 2-Chloroethyl Sulfide. Tertiary Butyl Chloroethiolacetate. Toxicity to Mice; Eye Effects on Animals*, April 14, 1943.
114. TDMR 619. *Efficacy of Certain Stabilizers for Levinstein HS in 75-mm. Shell*, April 7, 1943.
115. TDMR 646. *Preparation and Properties of bis(2-Chloroethyl) Selenide*, May 1, 1943.
116. TDMR 650. *Thickened Vesicants. Storage Stability of Unthickened and Thickened Purified Levinstein HS*, May 22, 1943.
117. TDMR 666. *The Effects of Mustard on Peritoneal Tissue*, May 28, 1943.
118. TDMR 669. *Levinstein Mustard. The Composition of Levinstein HS*, June 2, 1943.
119. TDMR 677. *The Vesicant Action of Sesquimustard and Certain Sesquimustard-type Compounds Submitted by Dr. W. A. Lazier*, June 12, 1943.
120. TDMR 682. *HQ(Sesquimustard — Mustard) Mixtures: LC_{50} for Mice*, June 15, 1943.
121. TDMR 688. *A Mixture of Mustard (HS) and Dichloroethylamine (ED) 50-50 by Weight: LC_{50} for Mice*, June 17, 1943
122. TDMR 692. *The Photosynthesis of Sesquimustard*, July 7, 1943.
123. TDMR 712. *HT 60/40, HQ 75/25, and H: Comparison by Toxicity to Mice, Vesicant Action on Men, and Penetration through Cloth*, August 2, 1943.
124. TDMR 721. *Agent Q. Evaluation of Raw Material for Production of HQ*, August 11, 1943.
125. TDMR 728. *A Photosynthetic Batch Process for the Manufacture of Q, bis(2-Chloroethylthio)ethane*, August 28, 1943.
126. TDMR 738. *Vapor Pressure of Pure Mustard*, September 13, 1943.
127. TDMR 743. *Levinstein Mustard. A Revision of the Theory in TDMR 669 on the Composition of Levinstein H*, September 28, 1943.
128. TDMR 746. *Stabilization of Levinstein H. Progress Report, Principally on Efficacy of Hexamethylenetetramine*, October 5, 1943.
129. TDMR 754. *The Photosynthesis of Dimustard, bis[2-(2-Chloroethylmercapto)ethyl] Sulfide*, October 16, 1943.
130. TDMR 763. *Stabilization of Levinstein H in One-ton Containers and 55-gallon Drums at Pine Bluff Arsenal*, November 5, 1943.

131. TDMR 786. *The Photosynthesis of T*, November 11, 1943.

132. TDMR 790. *Stabilization of Levinstein H, Volume and Density Changes Incident to Storage of Levinstein H in Steel*, January 4, 1944.

133. TDMR 791. *Stabilization of Levinstein H. The Rate of Corrosion of Steel by Levinstein H and by Levinstein H Stabilized with 1% Hexamethylenetetramine*, January 15, 1944.

134. TDMR 796. *Stabilization of Levinstein H. Some Variables Affecting the Stability of Plant-product Levinstein H and of Steam-distilled Levinstein H, and Their Corrosion of Metal Containers*, January 21, 1944.

135. TDMR 797. *Catalytic Studies on the Photosynthesis of Agent Q*, February 9, 1944.

136. TDMR 798. *Stabilization of Levinstein H. Properties of Levinstein H after Treatment with Ammonia Gas*, February 7, 1944.

137. TDMR 804. *Vapor Pressure Curves of Agents and Solvents*, February 26, 1944.

138. TDMR 808. *Further Studies in the Photosynthesis of Agent Q*, March 11, 1944.

139. TDMR 825. *Storage Stability of Alkali-treated and of Aerated Levinstein H*, April 10, 1944.

140. TDMR 831. *Thickened Vesicants. Storage Stability and Other Properties of Pure Grades of H when Thickened*, April 14, 1944.

141. TDMR 836. *Storage Stability of HQ. Stability of 25% Q in Levinstein H and in Steam-distilled H*, April 25, 1944.

142. TDMR 840. *The Photosynthesis of 2-Chloroethyl 2-Hydroxyethyl Sulfide*, May 3, 1944.

143. TDMR 846. *Efficiency of Certain Stabilizers for Levinstein H in 75-mm. Shell*, June 16, 1944.

144. TDMR 849. *Storage Stability of H Made by the TG Process and of H Obtained from Levinstein H*, June 14, 1944.

145. TDMR 852. *Storage Stability of Levinstein H in E-5 Bombs Coated with Herculite Lacquer*, June 12, 1944.

146. TDMR 853. *Stability of Levinstein H in Lacquered Containers*, June 14, 1944.

147. TDMR 872. *The Reduction of Light Energy Requirements in the Photosynthesis of Agent Q*, August 11, 1944.

148. TDMR 879. *Modified Vacuum Distillation Process for Purification of Levinstein H*, August 22, 1944.

149. TDMR 883. *Stabilization of Levinstein H. Pretreatment of Steel with Hexamethylene Tetramine to Retard Corrosion of the Steel by Levinstein H*, August 23, 1944.

150. TDMR 884. *Stabilization of Levinstein H. The Rate of Corrosion of Steel Test Pieces by Levinstein H as affected by the Ratio of Volume of Levinstein H to Area of Steel Surface*, August 26, 1944.

151. TDMR 886. *The Stabilization of Levinstein H. Storage Stability of Levinstein H, Stabilized and Unstabilized, at 50° and 65° C in 75-mm. and 155-mm. Shell and in Herculite-coated 10-lb. Bombs (M34)*, September 7, 1944.

152. TDMR 890. *Stabilization of Levinstein H*, September 20, 1944.

153. TDMR 899. *Stabilization of Levinstein H. Comparison of Hexamine, HN-1, and HN-3 as Stabilizers for Levinstein H in 75-mm. Shell*, October 2, 1944.

154. TDMR 905. *Stabilization of Levinstein H. Storage Stability of Levinstein H Pretreated with Alkali before Stabilizing with Hexamine*, October 13, 1944.

155. TDMR 908. *Stabilization of Levinstein H. Comparison of Test Results Obtained with Hexamine Powder, Granular Hexamine, and Hexamine Solution*, December 14, 1944.

156. TDMR 946. *Solubility of Q and of p-Dithiane in Vesicant Agents, and the Density of Liquid Q*, December 19, 1944.

157. TDMR 953. *Storage Stability at 65° C of Levinstein H in Containers of Various Sizes*, December 20, 1944.

158. TDMR 955. *Utilization of H-distillation Residues in the Manufacture of Levinstein H*, December 23, 1944.

159. TDMR 984. *Stability of Levinstein H and of HD under Cyclic Storage Conditions*, February 2, 1945.

160. TDMR 985. *Vacuum Distillation of Levinstein H: Pilot Plant Study*, March 17, 1945.

161. TDMR 989. *Solubility of Hydrogen Chloride in Mustard, and Effect on Pressure Stability*, February 14, 1945.

162. TDMR 1008. *Stability of Levinstein H. Effect of Water on Chemical and Pressure Stability of Levinstein H*, March 21, 1945.

163. TDMR 1031. *Corrosion by Vesicants: Rate of Corrosion of Steel and Other Metals by H, HQ, HN3, HN1, and L, Mostly at 65° C*, April 2, 1945.

164. TDMR 1036. *Stability of Levinstein H and of HD in Aluminum Containers*, April 14, 1945.

165. TRLR 18. *L, HN1, H, and HQ. Effects of 0.1 mg. Drops on Eyes of Rabbits*, December 20, 1943.

166. TRLR 35. *Mustard: LCt_{50} to Goats (10 Minute Exposure)*, June 6, 1944.

167. Field Progress Report No. 1, CWS Research and Development Program, Bushnell Installation. *Performance of the 500 lb. AC Bomb in Wooded Terrain*, March 13, 1944.

168. *Mustard Vapor Casualties Occurring at Bushnell, Florida, on April 20, 1944*. Dugway Proving Ground Mobile Field Unit, Bushnell, Fla., June 6, 1944.

169. Contract W-40-057-CWS-23, University of Chicago Toxicity Laboratory, Inf. Month. Prog. Rept. No. N.S. 2, May 15, 1945.

170. Contract W-285-CWS-5052, Monsanto Chemical Company, Final Report. *Development of Process for Manufacture of HQ from Thiodiglycol, 2-Mercaptoethanol, and HCl*, by J. Cooper, Jr., and H. F. McNell, Jr., July 31, 1944.

171. Contract W-285-CWS-5052, Monsanto Chemical Company, Final Report. *Development of a Process for the Manufacture of T from Thiodiglycol and HCl*, by J. Cooper, Jr. and H. F. McNell, Jr., November 10, 1944.

MISCELLANEOUS UNITED STATES REPORTS

172. *Mustard Gas*, by E. E. Reid, E. I. du Pont de Nemours and Company, September 15, 1942.

172a. F. Fogler, CWS, Hq. ETOUSA; Combined Intelligence Objectives Subcommittee, G-2 Division, SHAEF (Rear). *Continuous Processes for Production of Mustard Gas*, May 14, 1945.

UNITED STATES--UNITED KINGDOM REPORTS

Project Coordination Staff (Edgewood Arsenal)

173. PCS Report No. 9. *Résumé of Recent Knowledge on the Technical Aspects of Chemical Warfare in the Field*, May 17, 1945.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

174. Porton Memorandum No. 10A. *The Chemical Contamination of Water Supplies*, May 26, 1941.

175. Porton Memorandum No. 14. *The Production of Casualties in the Field by Weapons Charged Mustard Gas*, June 26, 1942.

176. Porton Memorandum No. 15. *Classified List of Compounds Examined Physiologically Since 1919*. October 1941 and addendum June 4, 1945.

177. Porton Memorandum No. 20. *Interim Memorandum on Gas Warfare in the Tropics*, November 21, 1944.

178. Porton Report No. 805. *Vapour Pressure of H*, March 28, 1931.

179. Porton Report No. 1104. *Report on the Physiological Examination of w, w'-Dichloro-β-Ethoxydiethyl Sulphide and 1,3-bis(β-Chloroethylthio)-2-Chloropropane*, May 5, 1933.

180. Porton Report No. 1110. *Stability of Mustard Gas. Note on a Reversible Decomposition by Heat*, June 23, 1933.

181. Porton Report No. 1367. *Preparation and Properties of T.804 (2,2',2''-tri(β-Chloroethylthio)triethylamine)*, May 23, 1935.

182. Porton Report No. 1731. *Report on the Physiological Examination of T.133*, June 17, 1937.

183. Porton Report No. 1737. *Laboratory Experiments on the Evaporation of Drops of SHS (30% Carbon Tetrachloride), HT (60 40), and HS*, June 14, 1937.

184. Porton Report No. 1885 (February 1938) and Addendum (May 1938), abridged and issued as CD Report No. 1002A, *The Estimated Effects Due to Enemy Air Attacks with Gas.*

185. Porton Report No. 2247. *The Chemistry of 2,2' Dichlorodiethyl Sulphide (H). Part IV*, August 1, 1941.

186. Porton Report No. 2280. *The Effects of Mustard Gas on Cities*, October 2, 1941.

187. Porton Report No. 2297. *The Effect of Mustard Gas Vapour on the Eyes*, November 8, 1941.

188. Porton Report No. 2343. *Medical Report on Casualties Produced by Airburst Mustard Gas Shell*, March 10, 1942.

189. Porton Report No. 2493. *The Physiological Effects of Various Substances on the Rabbit's Eye: A Preliminary Survey of Chemical Eye Injurants with Particular Reference to Molecular Structure and CW Potentialities* March 7, 1943.

190. Porton Report No. 2527. *The Measurement of the Thermal Conductivity of Mustard Gas*, July 24, 1943.

191. Porton Report No. 2537. *The Composition of Levinstein H*, September 17, 1943.

192. Porton Report No. 2561. *The Toxicity of Particulate Clouds of HN3 and H*, January 28, 1944.

193. Porton Report No. 2586. *Toxicity of H in Droplet Form*, February 3, 1944.

194. Porton Report No. 2612. *The Effects on Guinea Pigs of Exposing Them to Low Concentrations of H for Long Periods*, April 20, 1944.

195. Porton Report No. 2636. *The Reaction of Sodium Isethionate with Mustard Gas and with the Nitrogen Vesicants*, February 1, 1945.

196. Ptn.1000(S.145). *Report on the Re-examination of 1:3 di(β-Chloroethylthio)propane, 1:4 di(β-Chloroethylthio)butane, and 2:2'-Dichloro Diethyl Sulphide*, January 6, 1942.

197. Ptn.1200(R.9045). *Physiological Tests on Analogues of H*, July 23, 1941.

198. Ptn.1200(R.12035). *Comparative Vesicant Properties of Vesicant Compounds. Interim Statement*, October 3, 1941.

199. Ptn.1200(R.14727). *Comparative Vesicant Properties of Vesicant Compounds*, December 6, 1941.

200. Ptn.1201(R.7218). *Chemistry of 2,2'-Dichlorodiethyl Sulphide. Some Reactions of Vinyl Sulphoxide and Vinyl Sulphone*, June 6, 1941.

201. Ptn.1001A(V.1358). *Effects of H Vapour on Man*, February 7, 1945.

202. Ptn.1753(S.2867) *Report on the Physiological Examination of 18 Samples of β-Chloroethyl Sulfides*, March 3, 1942.

Research Establishment, Sutton Oak

203. S.O. R 496. *2,2'-Di(β-Chloroethylthio)diethyl Ether. Part IV. A Study of the Course of the HT Reaction. Interim Report*, January 8, 1941.

204. S.O. R 533. *2,2'-Di(β-Chloroethylthio)diethyl Ether. Part V. A Study of the Course of the HT Reaction. 2nd Interim Report*, June 10, 1941.

205. S.O. P 541. *2,2'-Di(β-Chloroethylthio)diethyl Ether. Part VI. The Higher Analogues of T.724*, August 2, 1941.

206. S.O. R 563. *2,2'-Di(β-Chloroethylthio)diethyl Ether. Part VII. The Impurities in Production HT*, December 29, 1941.

207. S.O. R 633. *2,2'-Di(β-Chloroethylthio)diethyl Ether. Part VIII. The Vapour Pressure*, January 12, 1943.

208. S.O. R 552. *The Freezing and Melting of Sulphur Dichloride*, October 23, 1941.

209. S.O. R 642. *The Phase Relations of War Materials and Intermediates. Part IV. The Freezing Point of the System: Compound of H and α-Methyl H*, February 9, 1943.

210. S.O. R 661. *The Phase Investigation of War Chemicals and Intermediates. Part V. The HM-S System*, May 19, 1943.

211. S.O. R 682 *A Physico-chemical Study of the HBD Reaction. Part I. Factors Influencing the Rate of Dissolution of Ethylene into Benzene*, September 30, 1943.

212. S.O. R 704. *A Physico-chemical Study of the HBD Reaction. Part II. The Kinetics of the HBD Reaction*, February 14, 1944.

213. S.O. R 459. *The Production of 1,2-di(β-Chloroethylthio)-ethane (Sesqui H) by a New Process. Part I. The Intermolecular Condensation of 2-Hydroxyethane-1-Thiol and Thiodiglycol.* (unlisted)

214. S.O. R 543. *The Production of 1,2-di(β-Chloroethylthio)-ethane (Sesqui H). Part II. Development of the HQ Process on the Laboratory Scale*, August 22, 1941.

215. S.O. R 523. *The Production of Low-Melting-Point Vesicants. Part I. Preliminary Survey of Possible Methods*, March 31, 1941.

216. S.O. R 547. *Low Melting Point Vesicants. Part II. Some Methyl Derivatives of H, T, Q, and Kindred Vesicants*, August 25, 1941.

217. S.O. R 567. *The Production of Low Melting Point Vesicants. Part III. Long-chain Vesicants of the Series* $ClC_2H_4S(CH_2)_nSC_2H_4Cl$, January 15, 1942.

218. S.O. R 618. *The Production of Low-melting-point Vesicants. Part IV. The Preparation of α-Methyl H*, September 24, 1942.

219. S.O. R 498. *Stability of HS, HM, and HMD. Part IV. Accelerated Pressure-stability Test for HM*, January 16, 1941.

220. S.O. R 501. *The Stability of HS, HM, and HMD. Part V. Prevention of SCl_2 H Reaction in HS*, February 14, 1941.

221. S.O. R 534. *Stability of HS, HM, and HMD. Part VI Correlation of Stability and Analytical Data*, June 30, 1941.

222. S.O. R 535. *Stability of HS, HM, and HMD. Part VII. Acceleration of the 100° C Standard Pressure Test*, June 7, 1941.

223. S.O. R 538. *Stability of HS, HM, and HMD Part VIII. The Chemical Causes of the Instability of HS and HM*, July 8, 1941.

224. S.O. R 558. *Stability of HS, HM, and HMD. Part IX. Interim Report on Stabilization by Ammonia and Ethylenediamine*, November 13, 1941.

225. S.O. R 578. *Stability of HS, HM, and HMD. Part X. The Stability of HMD*, March 30, 1942.

226. S.O. R 579. *Stability of HS, HM, and HMD. Part XI. Prestripping Treatment of Weak HS Liquor, Thermal Stabilization and Final Stabilization with Ammonia*, April 2, 1942.

227. S.O. R 529. *H-Sulphone: New Method of Production and Considerations on Its Possible Uses*, May 19, 1941.

228. S.O. R 545. *The Sulphur Dichloride Process for the Manufacture of Mustard Gas. Part XI. Examination of the Stability of Sulphur Dichloride*, December 18, 1941.

229. S.O. R 548. *The Mechanism of the Sulphur Dichloride-H Reaction*, August 26, 1941.

230. S.O. R 550. *The Methyl Thioethers of Vesicants of the Sulphur Group, Their Uses and Limitations as a Means of Analysis*, October 5, 1942.

231. S.O. R 551. *2,2'-Di(β-Chloroethylthio)diethyl Ether (T.724). Part II. Preparation and Physical Properties of T.724*, September 8, 1941.

232. S.O. R 577. *The Diffusion of 2,2'-Dichlorodiethyl Sulphide (H) in Still Air*, March 14, 1942.

233. S.O. R 584. *Manufacture of Lewisite HS. Operation of 0.2 Ton per Week Unit*, April 1, 1942.

234. S.O. R 615. *The Rate of Dissolution of 2,2'-Dichlorodiethyl Sulphide (H) in Distilled and Natural Waters*, August 25, 1942.

235. S.O. R 623. *A Survey of Processes for the Manufacture of H*, December 31, 1942.

236. S.O. R 683. *Vesicant Action and Molecular Structure*, October 18, 1943.

237. *Comparison of Proposed American BAL Plant, Described in OSRD No. 1531, with Existing Sutton Oak Unit*, September 14, 1943.

Extramural Research

238. Cambridge Extramural Testing Station (E. D. Adrian)
   a. XZ.144 (Y.19409A). *Third Survey of Toxicities of Fluoroacetates and Related Compounds*, December 20, 1943.
   b. XZ.152 (Y.23006). *Fourth Survey of Fluoroacetates and Related Compounds*, March 6, 1944.
   c. XZ.161 (Z.1032). *Determination of the LD_{50} for Five Quaternary Salts (XXVI)*, August 13, 1944.

239. Cambridge University (D. G. Cordier). V.3201. *Absorption through the Skin, and Systemic Effects of, Mustard Gas and Lewisite*, by D. G. Cordier, forwarded by the Chemical Board on May 19, 1941.

240. Cambridge University — Strangeways Research Laboratory (H. B. Fell). V.3853. *Report on the Biological Action of γ,γ'-Dichlorodipropyl Sulphide and T.224 as Compared with That of Dichlorodiethyl Sulphide*, by H. B. Fell, May 1941.

241. Cambridge University (H. McCombie)
   a. (V.1307). *Interim Report on Toxic Lead Compounds. Report No. 10*, by H. McCombie and B. C. Saunders, April 22, 1941.
   b. (V.5829). *1. Preparation of Toxic Lead Compounds of the Type $R{\cdot}SO_2NR'PbR_2'$. 2. Preparation of Aryl Lead Salts. 3. Preparation of Some Organic Tin Compounds. 4. (a) Preparation of Thallium Compounds of the Type R_2TlX. (b) Preparation of Mercury Compounds of the Type $RHgX$. (c) Preparation of Toxic Bismuth Compounds. (d) Diphenyl Antimonious Acetate*, by H. McCombie and B. C. Saunders, June 28, 1941.
   c. XZ.30 (Y.20189A). *Examination of Four Trialkyl Lead Sulphonamide Derivatives*, by H. McCombie, B. A. Kilby, and Margaret Thacker, January 8, 1941.
   d. XZ.61. *General Toxicity on Injection of Certain Sulphones and of a Dithian Derivative*, by M. McCombie, B. A. Kilby, and Margaret Kilby, August 16, 1941.
   e. XZ.95 (Y.24292A). *Physiological Examination of Trichloromethylsulfachloride and Trichloroacetyl Chloride*, March 3, 1942.
   f. XZ.101(W.3585). *The Physiological Examination of β,β-Di-(thiethyl)diethylmethylamine and diethyl thiocyanophosphate.* (undated)
   g. Y.15830. *Report No. 6 on Fluoroacetates and Allied Compounds*, September 30, 1943.
   h. Y.19184. *Report No. 8 on Fluoroacetates. β,β'-Difluoroethyl Ethylene Dithioglycol or Sesqui-fluoro-H. T.2019*, by H. McCombie and B. C. Saunders, November 30, 1943.

242. Oxford University — Department of Biochemistry (R. A. Peters)
   a. Report No. 49 (Y.20007). *On the Mechanism of the Physiological Action of Mustard: A Comparison of*

Some Properties of Mustard and Its Analogs, by E. R. Holiday and A. C. Ogston, January, 1942.

b. Report No. 65 (W19543). *The Preparation, Properties, and Toxicity of Purified DTH (BAL)*, January 29, 1943.

243. Oxford University – Dyson-Perrins Laboratory (R. Robinson)

a. Research Report No. 70. (V.19661A). *Notes on the Preparation of a Series of β-chloroethyl Sulphides*, by G. F. Harding, L. J. Goldsworthy, S. G. P. Plant and R. Robinson, November 22, 1941.

b. Research Report No. 71. (V.19661B). *Notes on the Preparation of Some β-chloro-ethyl-thio- Derivatives*, by G. F. Harding, W. L. Norris, B. Sabalewsky, L. J. Goldsworthy and S. G. P. Plant, January 13, 1942.

c. Ptn.1753(8.2867). *Report on the Physiological Examination of 18 Samples (β-Chloroethyl Sulphides)*, by R. Robinson, March 3, 1942.

d. (W.4200). *Collected Report No. 5 Embodying Reports Submitted During the 6 Months Ended April 30, 1942.*

244. University of Liverpool (A. Robertson)

a. U.528. *Synthesis and Properties of Vesicants by the HMD Reaction. Second Interim Report*, by A. Robertson, April 6, 1940.

b. U.9798. *Report on the Synthesis of Vesicants from Propylene and from Mixtures of Propylene and Ethylene Carried out at Liverpool University During the Period June 1, 1940 to July 31, 1940*, by A. Robertson, July 31, 1940.

245. University College, Southampton (N. K. Adam)

a. U.17886. *Vapour Pressure of Mustard*, by K. G. Denbigh and E. W. Baburn, December 5, 1940.

b. U.17886. *The Spreading of Chemical Warfare Agents on Fabrics and Permeability through Fabrics*, by K. R. Welsh, December 5, 1940.

c. V.380. *A Redetermination of the Vapour Pressure of Mustard Gas. Final Report*, by N. K. Adam, March 20, 1941.

MISCELLANEOUS BRITISH REPORTS

246. C.D.R.S 1.8. No. 75 A.4201. *Summary of Intelligence on Enemy CW and Smoke*, May 22 to June 6, 1945.

247. Porton Red Book. Chemical Defence Research Department, *Report on the Chemistry and Toxicity of Certain Compounds*, May 25, 1940, and Supplements.

CANADIAN REPORTS

Experimental Station, Suffield, Alberta

248. Suffield Report No. 118. *Storage of Levinstein HS in Bombs A C LI 500-lb. at Three Cycles (75-140° F) per Week*, September 1, 1944.

249. Technical Minute No. 7. *The Composition of American HS*, October 24, 1942.

250. Technical Minute No. 27. *The Physiological Properties of TL.258 (T.776 — 2-Chloro-1,3-bis(2-chloroethylthio)-propane)*, June 25, 1943.

251. Technical Minute No. 72. *A Comparison of the Erythema and Vesicle Producing Capacity of HT MM and HT*, September 15, 1944.

252. Technical Minute No. 74. *Storage of Levinstein HS in 50-gallon Drums*, September 16, 1944.

253. Technical Minute No. 80. *Comparison of the Relative Vesicancy of HTV CR, HTV MM, and HTV CR MM*, March 3, 1945.

Chemical Warfare Laboratories, Ottawa

254. CWL Report No. 17. *Purification of Levinstein HS by Solvent Extraction*, October 10, 1944.

255. Research Section Report No. 16. *Solvent Extraction of Levinstein HS. Preliminary Report*, February 3, 1943.

256. Research Section Report No. 19. *Purification of Levinstein HS by Solvent Extraction*, April 15, 1943.

Extramural Research

257. C. E. 81, Report No. 8. *Thickeners for Mustard. Molecular Weight Determinations on Purified Levinstein HS*, August 5, 1943, McGill University, Montreal.

258. C. E. 136, November 18, 1942. *Flash Distillation of HS (Levinstein). Preliminary Report*, by A. R. Gordon, G. J. Janz, and G. C. Benson, University of Toronto.

259. C. E. 136, December 18, 1942. *Flash Distillation of HS (Levinstein). Second Report*, by A. R. Gordon, G. J. Janz, and G. C. Benson, University of Toronto.

260. C. E. 136, February 23, 1943. *Flash Distillation of HS (Levinstein). Third Report*, by A. R. Gordon and G. J. Janz, University of Toronto.

261. C. E. 167, November 8, 1943. *Purification of HS (Levinstein) by Spray-carrier Distillation*, by A. R. Gordon and E. A. MacWilliam, University of Toronto.

OPEN LITERATURE

262. Bennett, G. M., *β,β'-Dichlorodiethyl Disulphide*, J. Chem. Soc., **119**, 418-425 (1921).

263. de Clermont et Wehrlin, Phillipe. *Sur Deux Nouvelles Urées Sulfurées*, Bl.[2] **26**, 125-127 (1876).

264. Conant, J. B., E. B. Hartshorn and G. O. Richardson, *The Mechanism of the Reaction Between Ethylene and Sulfur Chloride*, J. Am. Chem. Soc. **42**, 585-595 (1920).

265. Davies, J. S. H. and A. E. Oxford, *Formation of Sulphonium Chlorides and of Unsaturated Substances by the Action of Water and Aqueous Alcoholic Potash on β,β'-Dichlorodiethyl Sulphide*, J. Chem. Soc. 1931, 224-236.

266. Delepine, Fleury and Ville, *Recherches Sur Le Sulfure D'Éthyle β,β'-Dichloré*, Compt. Rendu **172**, 1238-1240 (1921).

267. Despretz, Ann. Chim. Phys. [2] **21**, 428 (1822).

268. Feloing, W. A. and S. B. Arenson, *The Precipitation of Sulfur from Crude Mustard Gas by Means of Ammonia*, Ind. Eng. Chem. **12**, 1005-1006 (1920).

269. Green, J., Soc. Chem. Ind. **38**, 363 R. (1919), **38**, 469 R (1919).

270. Guthrie, F. G., *On Some Derivatives from the Olefines*, Quart. Jour. Chem. Soc. **12**, 116-126 (1860).

271. Helfrich, O. B. and E. Emmett Reid, *Perchloro-Methyl-Mercaptan*, J. Am. Chem. Soc. **43**, 391-394 (1921).
272. Mann, F. G., W. J. Pope, and R. H. Vernon, *The Interaction of Ethylene and Sulphur Monochloride*, J. Chem. Soc. **119**, 634-646 (1921).
273. Meyer, Victor, *Weitere Studien Zur Kenntnis Der Thiophengruppe*, Ber. **19**, 628-632 (1886). *Ueber Thiodiglykolverbindungen*, Ber. **19**, 3259-3266 (1886).
274. Riche, Alfred, *Recherches Sur Des Combinaisons Chlorées Derivées des Sulfures de Méthyle et D'Éthyle*, Ann. Chim. Phys. [3] **63**, 283-304 (1855).
275. Schönberg, A., *A New Class of Free Radicals*, Trans., Faraday Soc. **30**, 17-18 (1934).
276. Schulze, Zeitschrift Für Chemie 1865, 78.
277. Vaughn, Wm. E. and Frederick Rust, *The Photo-Addition of Hydrogen Sulfide to Olefinic Bonds*, J. Org. Chem. **7**, 472 (1942).
278. Sartori, Mario, *The War Gases*, New York, D. Van Nostrand Co. Inc. 1939.

Chapter 6

OSRD FORMAL REPORTS

1. OSRD 833. *Corrosion of Steel, Brass and Solder by Pure 1070 and Pure 1130*, by Paul D. Bartlett, Harvard University, August 31, 1942. Div. 9-234.M4
2. OSRD 914. *Preparation and Stability Studies of 1130, 1070 and Closely Related Compounds*, by George H. Coleman, State University of Iowa, October 2, 1942. Div. 9-221.2-M2
3. OSRD 942. *The Beta-Chloroethylamines: Kinetics of Displacement, Hydrolysis, and Dimerization of Beta-Chloroethyldiethylamine, Methyl-bis-chloroethylamine and their Similarity to the Reactions of HS*, by Paul D. Bartlett Harvard University, October 7, 1942. Div. 9-221.1-M1
4. OSRD 981. *Summary of Work on 1070, 1130 and Related Compounds in Section B-3, NDRC*, by C. S. Marvel, The University of Illinois, October 22, 1942. Div. 9-221.2-M4
5. OSRD 1008. *The Stabilities of 1070 and 1130; Preparations and Properties of these Substances*, by M. S. Kharasch, University of Chicago, October 12, 1942. Div. 9-221.2-M3
6. OSRD 1045. *Volatility of Certain Arsenic and Nitrogen Compounds*, by H. E. Bent, November 10, 1942. Div. 9-200-M4
7. OSRD 1117. *The Preparation and Properties of Alkyl N-Nitroso-N-Alkylcarbamates and Related Compounds*, by M. S. Kharasch, University of Chicago, December 9, 1942. Div. 9-222.1-M1
8. OSRD 1131. *Summary of the Biochemical and Pharmacological Properties of the Amine Mustard*, by Homer W. Smith, New York University Medical School, December 9, 1942. Div. 9-321.1-M2
9. OSRD 1148. *The Preparation and Stability of 1143*, by George H. Coleman, State University of Iowa, December 7, 1942. Div. 9-221.2-M5
10. OSRD 1158. *The Preparation and Stability of 1149*, by George H. Coleman, State University of Iowa, December 9, 1942. Div. 9-221.1-M2
11. OSRD 1284. *Possible Toxic Agents and Intermediates*, by M. S. Kharasch, University of Chicago, March 22, 1943. Div. 9-200-M5
12. OSRD 1358. *The Preparation of β-Chloroethyl-β-Hydroxyethyl Methylamine and Its Polymerization Products*, by R. L. Shriner, University of Indiana, April 21, 1943. Div. 9-221.1-M4
13. OSRD 1438. *The Reactions of DH, TL 146, TL 320 and TL 145 with some Chemical Constituents of Biological Systems*, by Max Bergmann, W. H. Stein, J. S. Fruton, C. Columbic, and M. A. Stahmann, The Rockefeller Institute for Medical Research, May 21, 1943. Div. 9-361.3-M1
14. OSRD 1570. *The β-Chloroethylamines: A Further Kinetic Analysis of the Dimerization and Hydrolysis of Methyl bis-β-chloroethylamine: Further Observations on Diethyl-β-chloroethylamine and Tris-β-chloroethylamine*, by Paul D. Bartlett, Harvard University, July 6, 1943. Div. 9-221.1-M6
15. OSRD 1663. *The Volatilities, Vapor Pressures and Some Physical Constants of Twelve Nitrogen Mustards*, by C. Ernst Redemann, Ralph B. Fearing, and Dora Benedict, University of Chicago Toxicity Laboratory, August 2, 1943. Div. 9-221.1-M7
16. OSRD 1670. *The Preparation and Stability of Nitrogen Mustards*, by George H. Coleman, July 3, 1943. Div. 9-221.1-M5
17. OSRD 1855. *The Reactions of Nitrogen Mustards with Chemical Constituents of Biological Systems*, by Joseph S. Fruton and Max Bergmann, William H. Stein, Calvin Columbic, and Mark A. Stahmann, The Rockefeller Institute for Medical Research, September 28, 1943. Div. 9-321.1-M11
18. OSRD 1892. *A Kinetic Study of Ethyl-bis-β-chloroethylamine (HN-1) in Water-Acetone Solutions and a Comparison with Other β-Chloroethylamines*, by Paul D. Bartlett, C. Gardiner Swain, Sidney D. Ross, and James W. Davis, Harvard University, October 6, 1943. Div. 9-221.1-M8
19. OSRD 1960. *New Methods for Synthesizing Alkanolamines for Use in Vesicants. Exploratory Studies on the Synthesis of Ethanolamines from Formaldehyde and Hydrogen Cyanide*, by D. J. Luder, Ammonia Department, E. I. Du Pont de Nemours & Co., Inc., November 1, 1943. Div. 9-221.1-M1
20. OSRD 1961. *New Methods for Synthesizing Alkanolamines for use in Vesicants. Synthesis of Ethanolamines by Continuous Hydrogenation from Formaldehyde and Hydrogen Cyanide*, by D. J. Luder, E. I. du Pont de Nemours & Co., Inc., November 2, 1943. Div. 9-221.1-M2
21. OSRD 3354. *I. Preparation of Compounds Other than Nitrogen Mustards. II. Derivatives of CH Agents*, by George H. Coleman, Joseph E. Cullen, Joseph J. Carnes, Chester M. McCluskey, Ronald E. Pyle, Gust Nichols, Frank A. Stuart, and Robert L. Sundberg, State University of Iowa, March 14, 1944. Div. 9-200-M6
22. OSRD 3396. *Tests of Chloramnide-Containing Ointments for Protection and Decontamination of Human Skin Against Vesicants*, by Joseph Savit, John F. Thomson,

Eugene Goldwasser, Peter DeBruyn, and Margaret A. Bloom, University of Chicago Toxicity Laboratory, March 21, 1944. Div. 9-511-M2

23. OSRD 3351. *Preparation and Stability of the Nitrogen Mustards*, by George H. Coleman, Joseph E. Callen, Chester M. McCloskey, Gust Nichols, Ronald E. Pyle, Robert L. Sundberg, Frank A. Stuart, State University of Iowa, April 27, 1944. Div. 9-221.1-M10
24. OSRD 3557 *Studies on the Kinetics of the β-Chloroethylamines and their Products in Dilute Aqueous Solution*, by Barnett Cohen and Ervin R. Van Artsdalen, May 1, 1944. Div. 9-221.1-M11
25. OSRD 3621. *Treatment of Water Contaminated with Chemical Warfare Agents*, by A. M. Buswell, C. C. Price, A. C. Wiese, H. E. Hudson, and R. C. Gore, University of Illinois, May 13, 1944. Div. 9-561-M4
26. OSRD 3669. *The Chemistry of Three Nitrogen Mustards as Water Contaminants*, by Arthur M. Buswell and Charles C. Price, May 24, 1944. Div. 9-221.1-M12
27. OSRD 3928. *Storage Characteristics and Stabilization of HN-1 and HN-3*, by J. C. Woodhouse, A. S. Weygandt, M. T. Goebel, H. B. Fernald, Grasselli Chemical Department, E. I. du Pont de Nemours & Company August 1, 1944. Div. 9-221.1-M13
28. OSRD 3944. *A Vapor-train Study of the Comparative Vesicancy of Mustard and Several Related Amines and Sulfides on Human Skin*, by Simon Black, Kenneth P. DuBois, and Morris A. Lipton, University of Chicago Toxicity Laboratory, August 30, 1944. Div. 9-361.1-M1
29. OSRD 4176. *Status Report on Toxicity and Vesicant Tests of Compounds Referred to the University of Chicago Toxicity Laboratory*, by Hoylande D. Young, October 3, 1944. Div. 9-300-M4
30. OSRD 4194. *The Preparation for Toxicity Tests of Some Heterocycles Containing a Nitrogen Atom Common to Two Fused Rings*, by C. R. Noller and L. Kaplan, Stanford University, September 27, 1944. Div. 9-224-M3
31. OSRD 4273. *A Summary of the Vapor Pressures and Volatilities of Compounds Studied at the University of Chicago Toxicity Laboratory*, by C. Ernst Redemann, Saul W. Chaikin, Ralph B. Fenning, Drusilla Van Horsen, Joseph Savit, Dora Benedict, and George J. Rotariu, University of Chicago Toxicity Laboratory, November 4, 1944. Div. 9-200-M8
32. OSRD 4303. *The Preparation and Stability of Nitrogen Mustards and Related Compounds*, by George H. Coleman, Joseph E. Callen, Clinton A. Dornfeld, Chester M. McCloskey, Gust Nichols, Robert L. Sundberg, State University of Iowa, November 2, 1944. Div. 9-221.1-M15
33. OSRD 4333. *Chemical Reactions of the Nitrogen Mustards (Supplement to OSRD No. 1857)*, by Max Bergmann, Joseph S. Fruton, Calvin Columbie, Mark A. Stahmann, and William H. Stein, The Rockefeller Institute for Medical Research, January 2, 1945. Div. 9-221.1-M16
34. OSRD 4038. *Tests for Decontamination of Mustard and Nitrogen Mustards on Human Skin*, by Eugene Goldwasser, Peter P. H. DeBruyn, John F. Thomson, and Joseph Savit, University of Chicago Toxicity Laboratory, January 27, 1945. Div. 9-522-M4
35. OSRD 4681. *N-Substituted Carbamates of Phenols Containing a Quaternary Ammonium Group. II. Derivatives of Thymol and Carvacrol*, by R. L. Shriner, J. C. Speck, Jr., C. R. Russell, and W. H. Elliott, University of Indiana, February 5, 1945. Div. 9-222.4-M3
36. OSRD 4855. *The Penetration of Vesicant Vapors into Human Skin*, by Max Bergmann, Joseph S. Fruton, Calvin Columbie, Stephen M. Nagy, Mark A. Stahmann, and William H. Stein, Rockefeller Institute for Medical Research, March 24, 1945. Div. 9-361.1-M2
37. OSRD 5000. *The Effect of Flow Rate on the Toxicities of H, Q, HN1, and HN3 and L by Inhalation, by Total Exposure and by Body Exposure*, by Harry G. Albaum, Dora Benedict, Kenneth P. DuBois, Howard G. Ghent, James H. M. Henderson, and John O. Hutchens, University of Chicago Toxicity Laboratory. April 28, 1945. Div. 9-200-M1
38. OSRD 5003. *N-Alkyl Carbamates of 4-Substituted-3,5-Dimethylphenols*, by R. L. Shriner, C. R. Russell, and J. C. Speck, Jr., University of Indiana, April 28, 1945. Div. 9-222.1-M3
39. OSRD 5032. *A Formal Analysis of the Action of Liquid Vesicants on Bare Skin*, by Herbert D. Landahl, University of Chicago Toxicity Laboratory, May 5, 1945. Div. 9-360-M2
40. OSRD 5169. *Observations on the Role of Water in the Susceptibility of Human Skin to Vesicant Vapors*, by Buckey Renshaw, NDRC Division 9, June 1, 1945. Div. 9-361.1-M4
41. OSRD 5194. *Tests for Vesicancy on Human Skin*, by John F. Thomson, Hoylande D. Young, Joseph Savit, Eugene Goldwasser, Raymond G. Murray, and Peter DeBruyn, University of Chicago Toxicity Laboratory, June 1, 1945. Div. 9-300-M3
42. OSRD 5247. *Paraphenylenediamine Compounds*, by L. I. Smith and V. Engelhardt, University of Minnesota, June 25, 1945. Div. 9-321.3-M1
43. OSRD 5305. *Supplement to OSRD 4176, Status Report on Toxicity and Vesicant Tests of Compounds Referred to the University of Chicago Laboratory*, July 4, 1945. Div. 9-300-M5

OSRD INFORMAL REPORTS

44. Contract NDCrc-132. University of Chicago Toxicity Laboratory, E. M. K. Geiling. Inf. Month. Prog. Repts. *on Toxicity of Chemical Warfare Agents* (NDRC 9-4:1) Div. 9-123-M2

a. No. 1, February 16, 1943.
b. No. 3, April 10, 1943.
c. No. 5, June 10, 1943.
d. No. 10, November 10, 1943.
e. No. 13, February 10, 1944.
f. No. 17, June 10, 1944.
g. No. 18, July 10, 1944.
h. No. 19, August 10, 1944.
i. No. 20, September 10, 1944.
j. No. 21, October 10, 1944.
k. No. 22, November 10, 1944.
l. No. 23, December 10, 1944.
m. No. 24, January 10, 1945.
n. No 25, February 28, 1945.

45. Contract NDCrc-132, University of Chicago Toxicity Laboratory. Special Repts.
    a. No. 3. *Corneal Damage from TL 100 and TL 146*, August 14, 1942. Div. 9-326-M1
    b. No. 10. *I. Eye Effects and Toxicity of TL 329. II. Toxicity of 1070 for Mice*, October 31, 1942. Div. 9-327-M1
    c. No. 11. *Present Status of Comparative Effects of Amines and Carbamates on the Eye*, November 10, 1942. Div. 9-326-M2
    d. No. 15. *Present Status of Comparative Effects of Amines and Carbamates on the Eye*, November 23, 1942. Div. 9-326-M2
46. Contract NDCrc-130, Harvard University, P. D. Bartlett, Inf. Month. Prog. Repts. Div. 9-235-M11
    a. October 9, 1943.
    b. November 10, 1943.
    c. December 10, 1943.
    d. January 10, 1944.
    e. February 10, 1944.
    f. March 10, 1944.
47. Contract OEMsr-85, University of Nebraska, C. S. Hamilton. Inf. Month. Prog. Rept. for August 1943. Div. 9-213-M4
48. Contract OEMsr-97, Iowa State College, H. Gilman. Inf. Month. Prog. Repts. Div. 9-122-M1, M2
    a. May 1942.
    b. June 1942.
    c. April 1943.
    d. May 1943.
    e. July 1943.
    f. September 1943.
    g. January 1944.
49. Contract OEMsr-193, Indiana University, R. L. Shriner. NDRC 9:2:2 Informal Rept. No. 7. *N,N,N,N'-Tetra (β-Chloroethyl) Ethylene-diamine Dihydrochloride*, September 21, 1943. Div. 9-221.3-M1
50. Contract OEMsr-222, University of Chicago, M. S. Kharasch. Inf. Month. Prog. Rept., March 16, 1942. Div. 9-235-M2
51. Contract OEMsr-223, State University of Iowa, G. H. Coleman. Inf. Month. Prog. Repts. Div. 9-221.1-M2
    a. May 1942
    b. June 1942.
    c. September 1942.
52. Contract OEMsr-325, California Institute of Technology, E. H. Swift and Carl Niemann. NDRC 9:3, Inf. Rept. No. 97, *Tables of the Physical Constants of Chemical Warfare Agents*, June 5, 1944. Div. 9-200-M7
53. Contract OEMsr-394, University of Chicago, Morris S. Kharasch.
    a. NDRC 9:2:1 Informal Rept. No. 6. *Preparation of 2-Fluoroethyl Nitrocarbamates*, November 24, 1943. Div. 9-222.3-M1
    b. Inf. Month. Prog. Rept., September 1942.
    c. Inf. Month. Prog. Rept., December 1942.
    d. Inf. Month. Prog. Rept., January 1943.
    e. Inf. Month. Prog. Rept., February 1943.
    f. Inf. Month. Prog. Rept., April 1943.
    g. Inf. Month. Prog. Rept., May 1943.
    h. Inf. Month. Prog. Rept., June 1943.
    i. Inf. Month. Prog. Rept., January 1944.
    j. Inf. Month. Prog. Rept., April 1944.
54. Contract OEMsr-550, New York University, Homer W. Smith. Inf. Month. Prog. Rept., NDRC 9:5:1 No. 11, December 10, 1943. Div. 9-300-M1
55. Contract OEMsr-761, E. I. du Pont de Nemours and Company, H. W. Elley. Inf. Rept. No. 3, October 1, 1942.
56. Contract OEMemr-9, University of Pennsylvania, F. H. Adler.
    a. Rept. No. 37. *The Therapeutic Effect of Sodium Diethyl-Dithio-Carbamate Against HN3 Lesions of Rabbit Eyes*, by F. H. Adler, I. H. Leopold, and W. O. LaMotte, Jr., January 7, 1944. Div. 9-322.11-M4
    b. Rept. No. 38. *Pathology of Untreated HN3 Lesions of the Rabbit's Eye*, by F. H. Adler, W. E. Fry, I. H. Leopold, and W. O. LaMotte, Jr., January 10, 1944. Div. 9-322.2-M5
    c. Rept. No. 39. *The Pathology of a Standard Ocular Lesion of Liquid HN2*, by F. H. Adler, W. E. Fry, I. H. Leopold, and W. O. LaMotte, Jr., January 22, 1944. Div. 9-321.1-M13
57. Contract OEMemr-24, Wilmer Institute, The Johns Hopkins University, A. C. Woods and J. S. Friedenwald.
    a. Rept. No. 38. *Clinical and Pathological Studies on 1:30 Ocular Burns in the Rabbit*, by R. O. Schoch, August 26, 1943. Div. 9-321.2-M4
    b. Rept. No. 49. *A Comparison of the Histopathology of the Ocular Lesions Produced by Mustard and Nitrogen Mustards*, by A. E. Maumenee, April 14, 1944. Div. 9-301.3-M1
    c. Rept. No. 52. *Treatment of HN1, HN2, HN3 and TL 381 Ocular Injuries with Sodium Diethyl Dithiocarbamate, 4-Amino-3-mercapto benzoic acid and 4-Amino-3-mercapto benzoic acid ethyl ester*, by A. E. Maumenee, April 27, 1944. Div. 9-522.2-M4
    d. Rept. No. 59. *Treatment of HN2, HN1, HN3 and L Injuries of the Rabbit's Eye with Carbowax Ointments Containing NDR 902, NDR 620 or BAL or Mixtures of NDR 902 and BAL*, by J. S. Friedenwald and W. F. Hughes, Jr., August 12, 1944. Div. 9-522.2-M6

MISCELLANEOUS

58. Contract OEMsr-85, University of Nebraska, C. S. Hamilton. Correspondence, August 5, 1943. Div. 9-128-M1
59. Contract OEMsr-97, Iowa State College, Henry Gilman. Correspondence, April 7, 1942.
60. Contract OEMsr-394, University of Chicago, M. S. Kharasch. Correspondence:
    a. March 9, 1942
    b. December 11, 1942
    c. April 17, 1943
    d. June 21, 1945
61. Contract OEMsr-761, E. I. du Pont de Nemours and Company, H. W. Elley. Correspondence, August 30 1943.

62. Adler, F. H. and I. H. Leopold. *The Treatment of Vesicant Gas Injuries to the Eye After Decontamination*, Chapter 18 (pages 330-350) of Volume I, *Eye*, of the Fasciculus on *Chemical Warfare Medicine* prepared for the Committee on Medical Research of the Office of Scientific Research and Development by the Committee on Treatment of Gas Casualties of the Division of Medical Sciences of the National Research Council, 1945. Div. 9-110-M1

63. Schulz, R. O. *Clinical and Pathological Studies of Ocular Mustard Gas Burns*, Chapter 8 (pages 192-213) of Volume I, *Eye*, of the Fasciculus on *Chemical Warfare Medicine* prepared for the Committee on Medical Research of the Office of Scientific Research and Development by the Committee on Treatment of Gas Casualties of the Division of Medical Sciences of the National Research Council, 1945. Div. 9-110-M1

UNITED STATES ARMY REPORTS

Chemical Warfare Service

64. DPGSR 13. *Field Observations on Physiological Effect of HN-1*, August 23, 1943.

65. DPGSR 43. *Comparison of HN3 and Lewinstein H Dispersed in Open and Wooded Terrain Under Semi-tropical Conditions*, December 8, 1944.

66. DPGSR 52. *The A[illegible]ment of HN1 When Dispersed in Open Terrain Under Semi-tropical Conditions, and a Comparison of HN1, H, and HN3 Under these Conditions*, December 3, 1945.

67. EATR 78. *Constants and Physiological Action of Chemical Warfare Agents*, July 19, 1932.

68. EATR 281. *Tris(β-chloroethyl)amine and Tris(β-chloroethyl)amine Hydrochloride.*

69. HR(EA) 1. *The Clinical Aspects of Exposure to Nitrogen Mustard*, June 17, 1943.

70. MD(EA)MR 62. *Studies of Eye Lesions Caused by Compound 1130*, August 1, 1942.

71. Medical Division Report No. 40. *Evaluation of the Rabbit for HN1 Field Bioassay; LC_{50}, Symptomatology, Pathology, Hematology and Eye Studies*, July 7, 1945.

72. Medical Division Report No. 66. *The Protection Afforded by Class I M2 Zn(I) Processed CC-2 Impregnated Protective Clothing Against HN1 Vapor Under Simulated Tropical Conditions*, January 16, 1946.

73. Medical Division Report No. 67. *The Protection Afforded by Class II and Class I M2 Zn(I) CC-2 Impregnated Clothing Against HN3 Vapor Under Simulated Tropical Conditions*, January 24, 1945.

74. MIT-MR No. 49. *Manufacture of Bis(β-chloroethyl)-ethylamine by One-Step Process*, October 12, 1943.

75. MRL(EA) Rept. No. 23. *Correlation of Eye Changes in Rabbits with CT Exposure to H*, June 12, 1944.

76. TDMR 386. *Bis(2-chloroethyl)methylamine. Preliminary Physiologic Examination*, June 1, 1942.

77. TDMR 397. *Bis(2-chloroethyl)methylamine ("S"). Median Lethal Concentration for Mice*, June 20, 1942.

78. TDMR 423. *Tris(2-chloroethyl)amine. Physiological Examination*, August 12, 1942.

79. TDMR 431. *New Compounds: HN-2, KB-16, and HN-3. Field Tests in 105-mm. Shell in Comparison with HS*, September 3, 1942.

80. TDMR 435. *Tris(2-chloroethyl)amine: Preparation and Decontamination*. September 5, 1942.

81. TDMR 438. *Bis(2-chloroethyl)isopropylamine. Median Lethal Concentration for Mice (10-min. Exposure); Skin Irritant Action; Eye Effects*, September 21, 1942.

82. TDMR 442. *Bis(2-chloroethyl)methylamine. Preparation, Decontamination, and Stability*, September 28, 1942.

83. TDMR 458. *New Compounds. The Preparation of Bis(2-chloroethyl)isopropylamine*, October 25, 1942.

84. TDMR 464. *Bis(2-Chloroethyl)methylamine; Compound 1137; Mustard: Comparative Eye-action on Guinea Pigs*, November 4, 1942.

85. TDMR 521. *Triethylamine, 2,2'-dichloro-. LC_{50} for Mice, 10 Min. Exposure; Median Detectable Concentration; Vesicant Action; Penetration of Impregnated Cloth; Eye Effects*, December 26, 1942.

86. TDMR 537. *New Compounds. Detonation Tests on Chlor-Alkyl Amines Compared with HS, M-1 and ED*, January 26, 1943.

87. TDMR 552. *2,2'-Dichlorotriethylamine*, February 4, 1943.

88. TDMR 557. *2,2'-Dichlorotriethylamine. Effectiveness as an Airplane Spray*, February 6, 1943.

89. TDMR 564. *2,2'-Dichlorotriethylamine. Effectiveness in Explosive Munitions*, March 18, 1943.

90. TDMR 615. *Median Detectable Concentrations by Odor of Plant Run Mustard, Plant Run Lewisite, and Pilot Plant Ethyl Nitrogen Mustard*, April 16, 1943.

91. TDMR 656. *Nitrogen Mustards. Comparative Vesicant Action and Cloth Penetration*, May 28, 1943.

92. TDMR 665. *Development of Manufacturing Process for 2,2',2"-trichlorotriethylamine. Investigation of Conditions for Improving Process*, May 29, 1943.

93. TDMR 672. *2,2'-Dichlorotriethylamine. Effect of tracheotomy on rabbits exposed to high concentrations*, June 14, 1943.

94. TDMR 681. *Thickening of Nitrogen Mustards. Thickening of Mixtures of Lewinstein HS and Nitrogen Mustards. Thickening of Canadian HT.*

95. TDMR 683. *Pilot Plant Development of a Process for the Manufacture of HN-1*, July 1, 1943.

96. TDMR 686. *Pilot-plant Production of HN-3*, July 17, 1943.

97. TDMR 700. *The Manufacture of 2,2'-Dichlorotriethylamine (laboratory investigation)*, July 15, 1943.

98. TDMR 709. *The Manufacture of 2,2'-Dichlorotriethylamine. Effect of Quality of 2,2'-Dihydroxyethylamine*, July 20, 1943.

99. TDMR 785. *Manufacture of HN-1. Pilot Plant Development*, February 4, 1944.

100. TDMR 1031. *Corrosion by Vesicants: Rate of Corrosion of Steel and Other Metals by H, HQ, HN3, HN1, and L, Mostly at 65° C*, April 2, 1945.

101. TRLR 18. *L, HN-1, H and HQ. Effects of 0.1 mg. Drops on Eyes of Rabbits*, December 20, 1943.

102. TRLR 28. *Median Detectable Concentrations by Odor of Vacuum-distilled H, Thiodiglycol H, and Steam-distilled H*, April 12, 1944.

103. 42nd Chemical Laboratory Company. *Report No. 30*, March 8, 1943.
104. Medical Division Informal Monthly Progress Reports.
a. November 1944.
b. February 1945
c. March 1945.
d. April 1945.
e. September 1945.
105. Medical Research Laboratory (Edgewood Arsenal). Inf. Month. Prog. Rept. dated June 15, 1944.
106. Contract W-49-057-CWS-23, University of Chicago Toxicity Laboratory. Inf. Month. Prog. Repts. on *Toxicity and Irritancy of Chemical Agents.*
a. No. N.S. 2, May 15, 1945.
b. No. N.S. 4, July 15, 1945.
c. No. N.S. 6, September 15, 1945.
107. Jarman, G. N. *Report of Visit to Porton, March 16, 1943 Concerning HE Chemical Shell*, April 4, 1943.
107a. Memo from Bushnell Mobile Field Unit of the Dugway Proving Ground to Chief, Medical Division, OC-CWS, *Report on Mustard Vapor Casualties Occurring at Bushnell, Florida, April 20, 1944*, June 6, 1944.

UNITED STATES NAVY REPORTS

Naval Research Laboratory

108. NRL Report No. P-2364. *A Controlled Laboratory Experiment to Compare Lesions Resulting From Application of Mustard, Lewisite, and Nitrogen Mustards to the Skin of the Forearms of Humans*, September 1, 1944.
109. NRL Report No. P-2464. *Chamber Tests with Human Subjects. V. Arm Chamber Exposures to HN Vapors*, March 1945.
110. NRL Report No. P-2579. *Chamber Tests with Human Subjects. IX. Basic Tests with H Vapor*, August 14, 1945.
111. NRL Report No. P-2734. *Chamber Tests with Human Subjects. XVIII. Tests with HN Vapors*, January 9, 1946.

UNITED STATES—UNITED KINGDOM REPORTS

Project Coordination Staff (Edgewood Arsenal)

112. PCS Rept. No. 7. *Status Summary on the Relative Values of H, HN1, and HN3 as Bomb Fillings*, December 7, 1944.
113. PCS Rept. No. 9. *Résumé of Recent Knowledge on the Technical Aspects of Chemical Warfare in the Field*, May 17, 1945.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

114. Porton Memorandum No. 15. *Classified List of Compounds Examined Physiologically Since 1919*, October 1941, and *Addendum 1*, June 4, 1945.
115. Porton Memorandum No. 22. *Comprehensive Report on S*, March 5, 1943.
116. Porton Memorandum No. 24. *The Properties and C.W. Potentialities of T. 1702 (KB-16, Tl.486)*, April 24, 1943.
117. Porton Memorandum No. 28. *Methods of Decontamination*, April 15, 1944.
118. Porton Memorandum No. 30. *HN-3 as a C.W. Agent*, November 8, 1944.
119. Porton Report No. 2207. *Effect of Mustard Vapour on Human Eyes*, November 21, 1941.
120. Porton Report No. 2356. *The Chemistry of Methyl Bis-(β-Chloroethyl)-Amine ("N") and Related Compounds*, April 9, 1942.
121. Porton Report No. 2378. *Pathological Changes in Animals Exposed to S Vapour*, July 9, 1942.
122. Porton Report No. 2384. *The Chemistry of S and Related Compounds. Part II. A Preliminary Study of the Action of Water on S*, June 1942.
123. Porton Report 2402. *On the Action of S on the Eye; Its Comparison with Allied Compounds, and with H*, August 7, 1942.
124. Porton Report No. 2414. *T.1702. Preparation and Estimation*, August 31, 1942.
125. Porton Report No. 2415. *The Chemistry of S and Related Compounds. Part IV. The Synthesis of the Stereoisomeric Forms of S Dimer and S Chlorhydrin Dimer*, September 9, 1942.
126. Porton Report No. 2416. *The Chemistry of S and Related Compounds. Part V. The Preparation of S. Chlorohydrin* September 8, 1942.
127. Porton Report No. 2417. *The Chemistry of S and Related Compounds. Part VI. A Further Study of the Action of Water on S; the Attempted Isolation of the Neurotoxic Substance SB*, September 7, 1942.
128. Porton Report No. 2422. *The Dimerisation of S. Part I*, September 10, 1942.
129. Porton Report No. 2424. *S as a Water Contaminant*, September 8, 1942.
130. Porton Report No. 2454. *The Chemistry of S and Related Compounds. Part VII. Some Reactions of Ethylenimonium S; the Preparation of β,β'-Dimethyl S*, November 19, 1942.
131. Porton Report No. 2464. *Toxicity of S Vapour. Further Experiments on the Exposure of Animals to S Vapour*, February 9, 1943.
132. Porton Report No. 2469. *The Effects of Aqueous Solutions of S and its Reaction Products on the Eyes of Rabbits*, January 25, 1943.
133. Porton Report No. 2485. *A Method of Assessing Damage to the Uveal Tract Caused by S and Other C.W. Agents and Its Application to Determining the Comparative Effects of S and Its Products with Water*, February 24, 1943.
134. Porton Report No. 2493. *The Physiological Effects of Various Substances on the Rabbit's Eye: A Preliminary Survey of Chemical Eye Injurants with Particular Reference to Molecular Structure and C.W. Potentialities*, March 7, 1943.
135. Porton Report No. 2495. *The Chemistry of S. Part IX. Kinetics of Dimerisation and Alkaline Hydrolysis*, March 15, 1943.
136. Porton Report No. 2513. *The Chemistry of S and Related Compounds. Part XI. Ethyl-, n-Propyl-, and Isopropyl-bis(β-chloroethyl)amines*, June 9, 1943.

137. Porton Report No. 2523. *The Toxicity by Injection of Nitrogen Vesicants and Their Hydrolysis Products*, July 21, 1943.
138. Porton Report No. 2524. *The Dependence of the Severity of Eye Lesions on the Concentration of, and Time of Exposure to, S Vapour*, July 24, 1943.
139. Porton Report No. 2548. *Toxicity and Pathology of HN-3*, November 18, 1943.
140. Porton Report No. 2561. *The Toxicity of Particulate Clouds of HN-3 and H*, January, 1944.
141. Porton Report No. 2562. *The Toxicity of HN-3 in Droplet Form*, November 17, 1943.
142. Porton Report No. 2563. *The Effects of HN-1 Vapour on Human and Rabbit Eyes*, November, 1943.
143. Porton Report No. 2565. *Vapour Toxicity and Pathology of the Ethyl, n-Propyl and iso-Propyl Analogues of HN-3*, December 10, 1943.
144. Porton Report No. 2614. *The Toxicity of Aerosols of HN-3*, May 30, 1944.
145. Porton Report No. 2617. *The Stability of Production HN-2*, May 8, 1944.
146. Ptn. 1004 (R.14123). *Report on the Detectability by Smell, etc. of Trichlorotriethylamine (T.773)*, November 21, 1941.
147. Ptn. 1012 (T.136). *Shell Expenditure Necessary to Obtain and Maintain with (a) S and (b) H, a Concentration of Vapour Sufficient to Produce Eye Effects in a Given Time Over Similar Areas*, January 5, 1943.
147a. Ptn. 2800 (T.9832). *The Effect of Oily Drops on Eyes Exposed to Mustard Vapour*, August 9, 1944.
148. Ptn. 2805 (S.9517). *The Vesicant Power of Alkyl bis-(betachloroethyl)amines*, June 30, 1942.
149. Ptn. 2805 (T.2708). *Vesicant Power of HN-1*, March 2, 1944.
150. Ptn. 2805 (T.9834). *The Effect of Droplets of H and HN-3 on the Eyes of Rabbits*, August 12, 1944.
151. Ptn. 4300 (T.5810). *Comparative Rates of Hydrolysis of T.773, S and H*, May 3, 1943.
152. Ptn. 4385 (S.9125). *The Effects of T.773 on the Eyes of Rabbits*, July 14, 1942.
153. Ptn. 4386 (S.5005). *Use of S From the Air*, April 30, 1942.
154. Ptn. 4387 (S.10755). *Comparative Vesicant Power of T.773, S, and T.1793* August 1942.
155. Ptn. 4388 (T.7732). *Determination of Basic Data on the Rate of Evaporation of HN-1 in the Field*, July 22, 1944.
156. Chemical Defence Research Dept. *Report on the Chemistry and Toxicology of Certain Compounds* (Porton Red Book), May 25, 1940.

Research Establishment, Sutton Oak

157. S.O. R 575. *Laboratory and Semi-Scale Preparation of Trichlorotriethylamine*, March 7, 1942.
158. S.O. R 607. *N-Methyl-2,2'-Dichlorodiethylamine (S). Part I. Laboratory investigation of methods of preparation suitable for large-scale manufacture*, January 8, 1943.
159. S.O. R 630. *N-Methyl-2,2'-Dichlorodiethylamine (S). Part III. The Analysis of Crude S-Salt*, January 4, 1943.
160. S.O. R 631. *N-Methyl-2,2'-Dichlorodiethylamine (S). Part IV. Semi-technical Development of Processes for Manufacture of S-Salt and S*, January 20, 1943.
161. S.O. R 632. *N-Methyl-2,2'-Dichlorodiethylamine (S). Part V. The Continuous Preparation of S diol. Interim Report*, December 28, 1942.
162. S.O. R 636. *The Preparation of N-(β-Chloroethyl)-N-Nitrammethyl-Urethane (T.1762)*, January 20, 1943.
163. S.O. R 641. *N-Methyl-2,2'-Dichlorodiethylamine (S). Part VI. The Higher Homologues of S and S Diol*, February 9, 1943.
164. S.O. R 643. *2,2',2"-Trichlorotriethylamine (T.773). Part II. Physiochemical Properties of Pure T.773*, February 15, 1943.
165. S.O. R 653. *N-Methyl-2,2'-Dichlorodiethylamine (S). Part X. The Vapour-Liquid Equilibria of Binary Systems Encountered in the Production of S-diol*, March 26, 1943.
166. S.O. R 664. *N-Methyl-2,2'-Dichlorodiethylamine (S). Part XI. The Diffusion of S in Still Air*, May 24, 1943.
167. S.O. R 665. *Trichlorotriethylamine (T.773). Part III. The Physico-Chemical Properties of the Ethanolamines*, May 25, 1943.
168. S.O. R 668. *Trichlorotriethylamine (T.773). Part IV. Vapour-Liquid Equilibria of Binary Systems Containing Mono-, Di-, and Triethanolamines*, June 30, 1943.
169. S.O. R 669. *Trichlorotriethylamine (T.773). Part V. Dissociation Constants of the Ethanolamines, Surface Tensions and Thermal Data*, June 30, 1943.
170. S.O. R 691. *2,2',2"-Trichlortriethylamine. Part VI. Semi-technical preparation*, February 8, 1944.
171. S.O. DRR 692. *Preparation of 2:2':2" Trichlortriethylamine. Part VII. Design Memorandum for the Manufacture of 5 tons per week Crude Trichlortriethylamine*, January 18, 1944.
172. S.O. R 720. *The Preparation of 2,2',2"-Trichlortriethylamine. Part VIII. Distillation of Triethanolamine on a 5 tons week scale*, August 15, 1944.
173. S.O. R 724. *The Production of 2,2',2"-Trichlorotriethylamine. Part IX. Storage Trials on 2,2',2"-Trichlorotriethylamine*, July 31, 1944.
174. Y. 11450. *Full Report on the T.773 Accident at Research Establishment, Sutton Oak, March 1943*, August 24, 1943.
175. Y. 21305. *Severe H. Contamination. Toxic Vapour Casualties Due to S Vapour*, January 14, 1944.
176. *Report on Inquiry Concerning Incident at No. 2 Storage Vessel 'S' (HN-2) Plant*, December 23, 1943.

Extramural Research

177. Cambridge Extramural Testing Station (E. D. Adrian)
a. XZ.32 (U.20189C). *Examination of Di(β-Chloroethyl) Methylamine Hydrochloride*, by H. McCombie, B. A. Kilby, and M. Thacker, December 1, 1940.
b. XZ.98 (W.1712). *The Toxicity of "S" by Inhalation*, by H. McCombie, B. A. Kilby, M. Killy, and B. C. Saunders, April 20, 1942.
c. XZ.144 (U.19199A). *Third Survey of Toxicities of Fluoroacetates and Related Compounds*, by K. J. Carpenter and B. A. Kilby, December 20, 1943.
d. XZ.152 (Y.23096). *Fourth Survey of Fluoroacetates and Related Compounds*, by K. J. Carpenter and B. A. Kilby, March 6, 1944.
e. XZ.163 (Z.9291). *Examination of Two Fluorine*

Analogues of the Nitrogen Vesicants, by K. J. Carpenter and B. A. Kilby, August 31, 1944.

178. Cambridge University (H. McCombie). (Y.8850). *Rept. No. 5 on Fluoroacetates and Allied Compounds*, by H. McCombie and B. C. Saunders, September 30, 1943.

179. Imperial College, London (I. M. Heilbron)
   a. Report No. 15 (W.6054). *Some Analogues of S and T.773*, by I. M. Heilbron, E. R. H. Jones, G. Rose, and W. Wilson, June 30, 1942.
   b. Report No. 16. (W.14526 and covering letter W.14527). *Analogues of S and T.773*, by I. M. Heilbron, E. R. H. Jones, G. Rose, and W. Wilson, November 16, 1942.

180. Oxford Eye Hospital — Nuffield Laboratory of Ophthalmology (I. Mann)
   a. W.7794. *Interim Report on the Action of S (T.1024) on the Eye of the Rabbit*, by I. Mann, A. Pirie, and B. D. Pullinger, June 1942.
   b. W.11330. *Report on the Action of T.773 on the Eye of the Rabbit*, by I. Mann, B. D. Pullinger, and A. Pirie, September 1942.

181. Oxford University, Biochemical Laboratory (R. A. Peters)
   a. Report No. 54 (W.610). *The Reactions of T.1024 (S) in Aqueous Solution: With a Note on Velocity Constants of Hydrolysis of S and H*, by A. G. Ogston, April 4, 1942.
   b. Report No. 56 (W.7518). *Further Observations on the Reactions of S in Aqueous Solutions*, July 8, 1942.

182. Oxford University — Dyson Perrins Laboratory (R. Robinson)
   a. Research Report No. 73 (V.23562). *The Preparation of di-(β-chloroethyl)-methylamine*, by F. E. King and R. Robinson, March 14, 1942.
   b. Research Report No. 79 (W.7626). *Note on the Preparation of β-Chloroethyl Methyl Nitrosamine*, $Cl{\cdot}CH_2{\cdot}CH_2{\cdot}N(NO){\cdot}CH_3$, by L. J. Goldsworthy and R. Robinson, July 14, 1942.
   c. Research Report No. 80. *Note on the Preparation of N-Carbomethoxy-β-bromoethyl Nitrosamine*, $Br{\cdot}CH_2{\cdot}CH_2{\cdot}N(NO){\cdot}CO_2CH_3$, by L. J. Goldsworthy and R. Robinson, July 22, 1942.
   d. Research Report No. 89 (W.14753). *N-Ethyl-β,β'-Dichlorodiethylamine*, by G. A. Weeks, S. G. P. Plant, and R. Robinson, November 10, 1942.
   e. Research Report No. 122 (Z.4532). *β,β'-Difluorodiethylamine*, by A. W. Nineham, S. G. P. Plant, A. L. Tompsett, and R. Robinson, June 7, 1944.

183. University College, Southampton (N. K. Adam)
   a. V.390. *A Redetermination of the Vapour Pressure of Mustard Gas*, by N. K. Adam, March 29, 1941.
   b. W.205. *The Vapour Pressure of T.1024. The Melting Point of T.1024*, by E. W. Babson and N. K. Adam, April 1942.
   c. W.11451. *Vapour Pressure of T.773*, by N. K. Adam and E. W. Babson, September 28, 1944.

184. University of Edinburgh (J. M. Robson)
   a. W.10733. *The Effect of S Upon the Rabbit's Eye (S "Vapour Simulated" Lesions)*, by J. M. Robson and G. I. Scott, (not dated).
   b. W.17407. *The Effect of S Upon the Eyes of Rabbits (Second Report)*, by J. M. Robson, G. I. Scott, and W. J. B. Riddell, January 8, 1943.
   c. Z.9717. *Bacteriological Investigation of Infiltrative Lesions Developing in Eyes Contaminated with H and HN-3*, by J. M. Robson and A. A. B. Scott, October 21, 1944.
   d. Z.15824. *The Effect of Deliberate Infection of HN3 Lesions of the Rabbit's Eye, and the Value of Chemotherapy in these Conditions* by W. M. Levinthal, J. M. Robson, and A. A. B. Scott, February 2, 1945.

185. University of Manchester (A. R. Todd)
   a. Research Report No. 31 (W.812). *Preparation of N-Methyl Diethanolamine. Interim Report on S Production*, by A. R. Todd, R. E. Davies, H. T. Openshaw, and P. B. Russell, April 1942.
   b. Research Report No. 32 (W.2443). *Interim Report on S Production. The Preparation of S by the Action of Phosgene on N-Methyldiethanolamine*, by H. T. Openshaw, P. B. Russell, and A. R. Todd, May 8, 1942.
   c. Research Report No. 34 (W.6115). *On the Conversion of N-Methyldiethanolamine into N-Methyl-β,β'-dichlorodiethylamine by Treatment with Hydrochloric Acid*, by J. B. M. Herbert and A. R. Todd, June 1942.
   d. Research Report No. 37 (W.14303). *The Conversion of Methyldiethanolamine into S by Means of Phosgene*, by R. E. Davies, H. T. Openshaw, P. B. Russell, A. R. Todd, and J. Wardleworth, November 9, 1942.
   e. Research Report No. 39 (Y.2020), *Laboratory Experiments on the Continuous Production of S-1:1-diol*, by A. R. Gibson, A. R. Todd, and J. Wardleworth, April 1943.

MISCELLANEOUS

186. C.C.P. 4723. *Experiments in the Chamber to Determine What Concentration of H.S. Can be Recognised by Smell*, 1918.

187. V. 18200. *Commentary on the Aggressive Power of Trichlorethylamine*, by D. G. Cordier, (undated).

188. W.10033 (and correction W.11801). *Trichlorodiethylamine* (T.773), September 15, 1942.

CANADIAN REPORTS

189. Suffield Internal Report No. 2. *A Comparison of the Casualty-Producing Power of S and H Dispersed by Explosion*, January 15, 1943.

190. Suffield Report No. 61. *The Performance of the Bomb, L.C. A C 65 lb. Mk. I Charged S Under Winter Conditions*, May 17, 1943.

191. Suffield Technical Minute No 16. *Physiological Tests with S and Some Analogues of S. (a) A Comparison of the Efficiency of some A.G. Ointments as Antidotes for S. (b) Vesicant Properties of Some Analogues of S*, January 22, 1943.

192. Suffield Experimental Station, University of Alberta and Chemical Warfare Laboratories, Ottawa
   a. Suffield — *Sixth Interim Report on S*, July 8, 1942.
   b. Suffield — *Seventh Interim Report on S*, July 11, 1942.
   c. Chemical Warfare Laboratories — Research Section Report No. 10, *Interim Report on S: Methods of Detection.*
   d. C.E.110 — *Progress Report on S: Preparation of Methyl Dirthanol Amine; Preparation of S Hydrochloride; Stabilization: Tests for S*, May 1-July 1, 1942.
   e. University of Alberta — *Preparation of S·HCl*, by R. R. Sandin, July 2, 1942.
   f. University of Alberta — *Compound S-HCl-Hydrolysis*, July 16, 1942.
   g. University of Alberta — *Compound S-Detoxifying Agents*, July 22, 1942.

193. Chemical Warfare Laboratories, Ottawa. *Fourth Interim Report on S: The Use of Phosgene for the Conversion of Methyldiethanolamine into S*, by L. Marion and J. Colucci, September 23, 1942.

194. C.E.110. *Progress Report: Preparation of Methyldirthanolamine; Preparation of S Hydrochloride; Stabilization of S; Indicators for S; Treatment of S Burns*, by A. Eastwood, J. McAlpine and J. W. Burns, August 1942.

195. C.E.114. *The Kinetics of the Dimerization of S*, by C. A. Winkler, A. L. Thompson, and A. W. Hay, September 3, 1942.

196. C.E.115. *Progress Report: Preparation of β,β'-Dihydroxydiethylmethylamine; Preparation of S; Examination of the Quaternary Salt*, by G. F. Wright, H. H. Richmond, and A. F. McKay, May 1-June 1, 1942.

INDIAN REPORTS

196a. *The Effect of Mustard Gas Vapour on Eyes under Indian Hot Weather Conditions*, by J. S. Anderson, November 9, 1942.

AUSTRALIAN REPORTS

197. C. D. (Aust.) Rept. No. 33 *Trials with American Ointment M5*, May 1, 1944.

OPEN LITERATURE

198. Blicke, F. F., and Zienty, F. B. *Antispasmodics. III*, J. Am. Chem. Soc., **61**, 771 (1939).

199. Cope, Arthur C., and Hancock, Evelyn M. *Synthesis of 2-Alkylaminoethanols from Ethanolamine*. J. Am. Chem. Soc., **64**, 1503 (1942).

200. Mason, J. P. and H. W. Black. *Preparation and Polymerization of β-4-Morpholinoethyl Chloride*, J. Am. Chem. Soc. **62**, 1443 1448 (1940).

201. Mason, J. Philip, and Gasch, Dale J. *β,β',β"-Trichlorotriethylamine*. J. Am. Chem. Soc. **60**, 2816 (1938).

202. McCombie, H., and Purdie, D. *β,β',β"-Trichlorotriethylamine*. J. Chem. Soc. 1217 (1935).

203. Mohler, H., and Hämmerle, W. *Chemische Kampfstoffe XIX. Chemische und spektroskopische Eigenschaften von β,β',β"-Trichlor-triäthyl-amin (Hautgift) und dessen Hydrochlorid*. Helv. Chim. Acta, **23**, 1211 (1940).

204. Prelog, V., and Stepán, V. *Bis(β-halorthyl)amines. VII. A new synthesis of N-monoalkylpiperazines*. Coletion Czechoslov. Chem. Communications, **7**, 93-102 (1935), Chem. Abstr. **29**, 4013 (1935).

205. Ward, Kyle, Jr. *The Chlorinated Ethylamines — A New Type of Vesicant*. J. Am. Chem. Soc., **67**, 914 (1935).

206. *Ringschliessung unter Ersatz zweier benachbarter Wasserstoffatome*. Fiebeh, Ber., **74B**, 1443 (1941).

207. *Piperidine Derivatives*. I. G. Farbenindustrie, A.-G. Brit. 501, 135, February 21, 1939. Chem. Abstr. **33**, 5872 (1939).

Chapter 7

OSRD FORMAL REPORTS

1. OSRD 108. *Preparation of Certain Organic Arsenicals*, by C. S. Hamilton, University of Nebraska, June 27, 1941. Div. 9-213-M1

2. OSRD 113. *Compounds Prepared for the Chemical Warfare Service by the National Defense Research Committee as of June 1, 1941*, by Roger Adams, Homer Adkins, P. D. Bartlett, Henry Gilman, C. S. Hamilton, C. D. Hurd, and C. S. Marvel. Div. 9-200-M1

3. OSRD 118. *Economies in the Preparation of DM*, by P. D. Bartlett, Harvard University, July 31, 1941. Div. 9-213.14-M1

4. OSRD 129. *The Preparation of 5,10-Dichloro 5,10-Dihydroarsanthrene*, by C. S. Hamilton, University of Nebraska, September 4, 1941. Div. 9-213.22-M1

5. OSRD 149. *Problems on Arsenicals*, by C. S. Hamilton, University of Nebraska, October 8, 1941. Div. 9-213-M2

6. OSRD 190. *Improved Methods for the Manufacture of Lewisite*, by P. D. Bartlett, Harvard University, December 9, 1941. Div. 9-213.11-M1

7. OSRD 314. *Preparation of Organometallic Compounds as Sources of Toxic Oxide Smokes and Flame Thrower Fuels*, by Henry Gilman, Iowa State College, January 9, 1942. Div. 9-210-M1

8. OSRD 326. *Preparation of Cacodyl and Cacodyl Chloride*, by C. S. Marvel and R. C. Fuson, University of Illinois, January 19, 1942. Div. 9-213.13-M1

9. OSRD 401. *Potentiometric Titration of Small Amounts of M-1, HS, ED or DM*, by J. H. Northrop, Rockefeller Institute for Medical Research, February 21, 1942. Div. 9-422.8-M2

10. OSRD 402. *Reaction of M-1 (Lewisite) with Dithiols and Other Thio Agents*, by P. D. Bartlett, Harvard University, February 20, 1942. Div. 9-213.11-M2

11. OSRD 407 *Improved Methods for the Manufacture of M-1 (Lewisite)*, by P. D. Bartlett, Harvard University, February 23, 1942. Div. 9-213.11-M3

12. OSRD 408. *The M-1 Oxides (β-Chlorovinylarsine Oxide). The Preparation of Slightly Impure Isomer I Oxide and Pure Isomer II Oxide*, by P. D. Bartlett, Harvard University, February 25, 1942. Div. 9-213.11-M4

13. OSRD 443. *Preparation of Radiometric Adamsite and*

Mustard, by G. B. Kistiakowsky, Harvard University, March 20, 1942.

14. OSRD 460. *Urea Peroxide as a Possible Decontaminant for M-1 and HS*, by P. D. Bartlett, Harvard University, March 28, 1942. Div. 9-312-M1
15. OSRD 470. *The Geometrical Isomers of M-1 (Lewisite)*, by P. D. Bartlett, Harvard University, March 31, 1942. Div. 9-213.11-M5
16. OSRD 493. *Detection of HS, M-1, ED or PDA with Trained Dogs and Rats*, by J. H. Northrop, Rockefeller Institute for Medical Research, April 10, 1942. Div. 9-422.8-M3
17. OSRD 507. *Catalytic Production of Homologs of Carvyl and Their Derivatives*, by R. C. Fuson and C. S. Marvel, University of Illinois, April 15, 1942. Div. 9-213.13-M2
18. OSRD 516. *Volumetric Methods for the Determination of Small Quantities of HS, Q, T, M-1, ED, DM and PDA*, by J. H. Northrop, Rockefeller Institute for Medical Research, April 20, 1942. Div. 9-422.8-M4
19. OSRD 570. *Amplifier to Replace Galvanometer in Potentiometric Titration of Small Amounts of M-1, HS, ED or DM*, by J. H. Northrop, Rockefeller Institute for Medical Research, May 15, 1942. Div. 9-413.1-M1
20. OSRD 580. *Constant Flow Micro-Apparatus for Exposure of Mice to Volatile Toxic Agents under Controlled Conditions*, by E. M. K. Geiling, University of Chicago, May 20, 1942. Div. 9-372-M2
21. OSRD 655. *Thickening of M-1*, by P. D. Bartlett and C. G. Swain, Harvard University, June 10, 1942. Div. 9-213.11-M6
22. OSRD 667. *The Thickening of HS-M-1 Mixtures, and a Photographic Study of the Impact of HS Drops on Cloth*, by Rockefeller Institute for Medical Research, June 15, 1942. Div. 9-210-M1
23. OSRD 733. *Arsine: (1) Median Lethal Concentration for White Mice. (2) Effect of High Concentrations for Short Exposures*, by E. M. K. Geiling, University of Chicago, July 20, 1942. Div. 9-313.1-M1
24. OSRD 749. *A Study of Peroxides Suitable for the Treatment of M-1 Burns*, by M. S. Kharasch, University of Chicago, July 24, 1942. Div. 9-312-M2
25. OSRD 786. *Furan Arsenicals*, by C. S. Hamilton, University of Nebraska, August 12, 1942. Div. 9-213.12-M1
26. OSRD 799. *The Corrosion of Steel by M-1 (Lewisite)*, by P. D. Bartlett, Harvard University, August 14, 1942. Div. 9-254-M1
27. OSRD 823. *Toxic Effects of Various Arsine Derivatives*, by E. M. K. Geiling and F. C. McLean, University of Chicago, August 24, 1942. Div. 9-313.1-M2
28. OSRD 824. *A Study of the Preparation of the Amyldichloroarsines*, by R. C. Fuson, University of Illinois, August 20, 1942. Div. 9-213.14-M2
29. OSRD 825. *The Corrosion of Steel by 50°; HS 50°; M-1 Mixture*, by P. D. Bartlett, Harvard University, August 24, 1942. Div. 9-254-M2
30. OSRD 834. *The Reaction of M-1 (Lewisite) with Amines. The Preparation of M-1 Dithiazide (Dithazyl-β-Chlorovinylarsine)*, by P. D. Bartlett, Harvard University, August 26, 1942. Div. 9-213.11-M7
31. OSRD 835. *The Corrosion of Steel by 50°; HS (TG)-50°; M-1 (Ref'd) Mixture*, by P. D. Bartlett, Harvard University, August 31, 1942. Div. 9-254-M5
32. OSRD 837. *Aliphatic Dichloroarsines*, by C. S. Hamilton, University of Nebraska, August 28, 1942. Div. 9-213.14-M3
33. OSRD 839. *The Reaction of M-1 (Lewisite) with Thiols. The Reaction of M-2 with Ethanedithiol*, by P. D. Bartlett, Harvard University, August 26, 1942. Div. 9-213.11-M8
34. OSRD 846. *Preparation of Cadmium Salts and Organocadmium Compounds*, by Henry Gilman, Iowa State College, August 26, 1942. Div 9-215-M1
35. OSRD 850. *The Reactions of n-Amyl-, Isoamyl-, and n-Hexyldichloroarsines in Comparison with Lewisite*, by P. D. Bartlett, Harvard University, September 4, 1942 Div. 9-213 14-M4
36. OSRD 864. *Titration of HS, Q, T, M-1, ED and PDA with Hypochlorite and Methyl Red*, by J. H. Northrop, Rockefeller Institute for Medical Research, September 7, 1942. Div. 9-422.8-M7
37. OSRD 867. *Preparation of Radioactive Lewisite*, by G. B. Kistiakowsky, Harvard University, August 31, 1942. Div. 9-213.11-M9
38. OSRD 878. *Summary Report on Work Done on Chemical Warfare Problems at the University of Illinois*, by C. S. Marvel and R. C. Fuson, University of Illinois, September 11, 1942. Div. 9-200-M2
39. OSRD 901. *Annual Report on Organic Arsenicals*, by C. S. Hamilton, University of Nebraska, November 3, 1942. Div. 9-213-M3
40. OSRD 1045. *Volatility of Certain Arsenic and Nitrogen Compounds*, by H. E. Bent, University of Missouri, November 10, 1942. Div. 9-200-M4
41. OSRD 1052. *Status Report on Toxicity and Vesicant Tests of Compounds Referred to the Chicago Toxicity Laboratory through November 4, 1942*, by E. M. K. Geiling, University of Chicago, December 2, 1942. Div. 9-300-M3
42. OSRD 1075. *The Production of Lewisite by the Mercuric Chloride Process. Investigation of the Effects of Impurities in Arsenic Trichloride*, by P. D. Bartlett, Harvard University, December 7, 1942. Div. 9-213.11-M10
43. OSRD 1109. *A Comparison of the Lethal Effects of Several Dichloroarsines on Mice Exposed to the Vapors at Low Relative Humidity*, by J. O. Butcher, W. L. Doyle, R. Merrill, H. G. Glass, and C. C. Lushbaugh, University of Chicago Toxicity Laboratory, February 16, 1943. Div. 9-313.1 M2
44. OSRD 1200. *A Toxicity Study of Several Furan Derivatives*, by G. J. Rotariu, M. A. Lipton, S. Black, J. O. Butcher, and C. C. Lushbaugh, University of Chicago Toxicity Laboratory, February 16, 1943. Div. 9-313.2-M1
45. OSRD 1253. *Toxic Effects of Various Arsine Derivatives III. Lethal Effects Produced by Absorption of Vapor of Dichloro(2-Chlorovinyl)arsine and Dichloroethylarsine through the Skin of Dogs, Cats, Rats, Rabbits, Guinea Pigs, and Mice*, by J. O. Butcher, H. G. Glass, H. W. Gurney, and R. Merrill, University of Chicago Toxicity Laboratory, March 11, 1943. Div. 9-313.1-M4
46. OSRD 1261. *Production of Sulfur Monochloride and Thionyl Chloride without the Use of Elemental Chlorine*,

by E. I. du Pont de Nemours and Company, March 19, 1943. Div. 9-212.2-M6

47. OSRD 1284. *Possible Toxic Agents and Intermediates*, by M. S. Kharasch, University of Chicago, March 30, 1943. Div. 9-200-M5

48. OSRD 1294. *The Preparation of Ethyldichloramine and Related Compounds*, by M. S. Kharasch, University of Chicago, April 1, 1943. Div. 9-213.14-M5

49. OSRD 1328. *Toxic Effects of Various Arsine Derivatives IV. Toxic Effects of Certain Nitrophenyldichloroarsines*, by E. M. K. Geiling and F. C. McLean, University of Chicago, April 15, 1943. Div. 9-313.1-M5

50. OSRD 1378. *Use of Crude White Arsenic in Present Chemical Warfare Service Arsenic Trichloride Process*, by J. C. Woodhouse, E. I. du Pont de Nemours and Company, May 5, 1943. Div. 9-213.21-M1

51. OSRD 1381. *Arsenic Trichloride, Laboratory Study of Manufacture by the Use of Hydrogen Chloride*, by J. C. Woodhouse, E. I. du Pont de Nemours and Company, May 10, 1943. Div. 9-213.21-M2

52. OSRD 1390. *Perazides Suitable for the Treatment of M-1 Burns*, by M. S. Kharasch and S. Weinhouse, University of Chicago, May 17, 1943. Div. 9-512-M3

53. OSRD 1444. *Determination of HS, M-1 and Other Gases in Air, at a Distance from the Operator*, by J. H. Northrop, Rockefeller Institute for Medical Research, May 29, 1943. Div. 9-422.8-M9

54. OSRD 1516. *Behavior of Chemical Agents M-1, HS, MS and FS upon Storage in Contact with Monel Metal*, by J. C. Woodhouse, E. I. du Pont de Nemours and Company, June 24, 1943. Div. 9-254-M6

55. OSRD 1553. *Production of M-1 by the Mercuric Chloride Process, Acceleration of Rate of Absorption and M-1 Production by Metallic Chloride Catalysts*, by P. D. Bartlett, H. J. Dauben, and L. J. Rosen, Harvard University, July 10, 1943. Div. 9-213.11-M11

56. OSRD 1594. *The Preparation of Ethyl Dichloroarsine on a Pilot Plant Scale*, by Jackson Laboratory, E. I. du Pont de Nemours and Company, July 19, 1943. Div. 9-213.14-M6

57. OSRD 1752. *Use of Crude White Arsenic in Present Chemical Warfare Service Trichloride Process*, by Grasselli Chemicals Department, E. I. du Pont de Nemours and Company, September 15, 1943. Div. 9-213.21-M1

58. OSRD 1797. *Organic Arsenicals*, by C. S. Hamilton, University of Nebraska, September 25, 1943. Div. 9-213-M5

59. OSRD 1911. *Determination of the Distribution of H and L in Skin and Eye Tissues by Radio-Autographic Techniques*, by J. C. Hamilton, University of California, October 23, 1943. Div. 9-362-M2

60. OSRD 3112. *Automatic Titrator for the Determination of H, L and Other Gases in Air*, by J. H. Northrop, Rockefeller Institute for Medical Research, January 17, 1944. Div. 9-413.1-M2

61. OSRD 3305. *The Mechanism of the Formation of Lewisite in the Mercuric Chloride Process*, by P. D. Bartlett, J. Dauben, Jr., L. J. Rosen, and S. D. Ross, Harvard University, March 28, 1944. Div. 9-213.11-M12

62. OSRD 3367. *Use of Crude White Arsenic in a Chemical Warfare Service Arsenic Trichloride Plant*, by J. C. Woodhouse, E. I. du Pont de Nemours and Company, March 29, 1944. Div. 9-213.21-M3

63. OSRD 3386. *Tests of Chloramide-Containing Ointments for Protection and Decontamination of Human Skin against Vesicants*, by J. Savit, J. F. Thomson, E. Goldswasser, P. DeBruyn, W. Bloom, E. M. K. Geiling, University of Chicago, April 6, 1944. Div. 9-511-M2

64. OSRD 3428. *Synthesis of Organic Arsenicals from Unsaturated Compounds*, by W. A. Lazier and S. L. Scott, E. I. du Pont de Nemours and Company, July 13, 1944. Div. 9-213-M7

65. OSRD 3501. *Tests for Decontamination of Lewisite on Human Skin*, by J. F. Thomson, E. Goldswasser, J. Savit, E. M. K. Geiling, R. K. Cannan, and W. Bloom, University of Chicago, April 28, 1944. Div. 9-523-M2

66. OSRD 3942. *Protective Clothes: I. Irritancy of Vapor-Contaminated Samples on Human Skin: II. Penetration of Vapor and Liquid Vesicants*, by J. Savit, E. Goldswasser, J. F. Thomson, and R. S. Merrill, University of Chicago Toxicity Laboratory, August 30, 1944. Div. 9-540-M1

67. OSRD 4051. *Selenides*, by C. D. Hurd, Northwestern University, August 22, 1944. Div. 9-214-M1

68. OSRD 4176. *Status Report on Toxicity and Vesicant Tests of Compounds Referred to the University of Chicago Toxicity Laboratory*, by E. M. K. Geiling, R. K. Cannan, W. Bloom, and H. D. Young, University of Chicago, October 3, 1944. Div. 9-300-M4

69. OSRD 4193. *The Chemistry of Certain Arsenical Chemical Warfare Agents as Water Contaminants*, by A. M. Buswell, C. C. Price, R. M. Roberts, C. W. Smith, and B. H. Velsen, University of Illinois, June 26, 1944. Div. 9-213-M6

70. OSRD 4273. *A Summary of the Vapor Pressures and Volatilities of Compounds Studied at the University of Chicago Toxicity Laboratory*, by C. E. Redemann, J. Savit, G. J. Rotariu, and R. B. Fearing, University of Chicago, November 4, 1944. Div. 9-200-M8

71. OSRD 4310. *Automatic Titrator for the Determination of H, L and Other Gases in Air. Supplement #4*, by J. H. Northrop and J. F. Gettemans, Rockefeller Institute for Medical Research, October 31, 1944. Div. 9-422.8-M12

72. OSRD 4311. *Determination of HS, M-1 and Other Gases in Air at a Distance from the Operator. Supplement #2*, by J. H. Northrop and J. F. Gettemans, Rockefeller Institute for Medical Research, October 31, 1944. Div. 9-422.8-M13

73. OSRD 4333. *Organic Arsenicals and Other Toxic Agents*, by C. S. Hamilton, E. J. Crogue, R. J. Andrew, R. F. Coles, and B. Ehern, University of Nebraska, January 1, 1945. Div. 9-219-M4

74. OSRD 4585. *A New Chamber for the Determination of Toxicities by Total, Body or Head Exposure*, by R. S. Merrill, H. G. Glass, E. M. K. Geiling, W. Bloom, and R. K. Cannan, University of Chicago, January 17, 1945. Div. 9-372-M5

75. OSRD 4854. *A Search for Decontaminating and Treatment Agents for Skin Exposed to Mustard Gas, II*, by P. D. McMaster, G. H. Hogeboom, and M. B. Sulzberger, Rockefeller Institute for Medical Research, March 24, 1945. Div. 9-522.12-M21

76. OSRD 4880. *Pilot Plant for Arsenic Trichloride Using Hydrogen Chloride Process*, by J. C. Woodhouse, O. L. Thomas, and L. A. Myers, E. I. du Pont de Nemours and Company, April 1, 1945. Div. 9-213.21-M4

77. OSRD 5000. *The Effect of Flow Rate on the Toxicities of H, Q, HN-1, HN-3 and L by Inhalation, by Total Exposure and by Body Exposure*, by K. P. DuBois, J. O. Hutcheon, E. M. K. Geiling, and R. K. Cannan, University of Chicago, April 28, 1945. Div. 9-300-M1

78. OSRD 5032. *A Formal Analysis of the Action of Liquid Vesicants on Bare Skin*, by A. D. Landahl, W. Bloom, R. K. Cannan, and E. M. K. Geiling, University of Chicago, May 5, 1945. Div. 9-300-M2

79. OSRD 5194. *Tests for Vesicancy on Human Skin*, by J. Savit, E. Goldswasser, E. M. K. Geiling, and R. K. Cannan, University of Chicago, June 1, 1945. Div. 9-300-M3

80. OSRD 5305. *Supplement to OSRD #176, Status Report on Toxicity and Vesicant Tests of Compounds Referred to the University of Chicago Laboratory*, by W. Bloom, R. K. Cannan, and E. M. K. Geiling, University of Chicago, July 4, 1945. Div. 9-300-M5

81. OSRD 5561. *Vapor Phase Synthesis of Lewisite*, by W. A. Lazier, P. L. Salzberg, and S. L. Scott, E. I. du Pont de Nemours and Company, September 7, 1945. Div. 9-213.11-M13

OSRD INFORMAL REPORTS

82. Contract NDCrc-132, University of Chicago (University of Chicago Toxicity Laboratory). Inf. Month. Prog. Repts. Div. 9-125-M2
- a. No. 1, February 10, 1943.
- b. No. 3, April 10, 1943.
- c. No. 4, May 10, 1943.
- d. No. 5, June 10, 1943.
- e. No. 6, July 10, 1943.
- f. No. 7, August 10, 1943.
- g. No. 8, September 10, 1943.
- h. No. 9, October 10, 1943.
- i. No. 10, November 10, 1943.
- j. No. 11, December 10, 1943.
- k. No. 12, January 10, 1944.
- l. No. 15, April 10, 1944.
- m. No. 16, May 10, 1944.
- n. No. 17, June 10, 1944.
- o. No. 20, September 10, 1944.
- p. No. 22, November 10, 1944.

83. Contract NDCrc-169, Harvard University, A. R. Moritz and F. C. Henriques, Jr. Inf. Month. Prog. Repts. Div. 9-312.13-M4
- a. Rept. (NDRC B4-C) of August 18, 1942.
- b. Rept. (NDRC B4-C) of October 17, 1942.
- c. Rept. (NDRC B4-C) of November 19, 1942.
- d. Rept. (NDRC B4-C) of December 19, 1942.

84. Contract OEMsr-97, Iowa State College, Henry Gilman. Inf. Month. Prog. Repts. Div. 9-122-M1 Div. 9-122-M2 Div. 9-122-M3
- a. December 1941.
- b. February 1942.
- c. April 1942.
- d. August 1942.
- e. September 1942.
- f. October 1942.
- g. November 1942.
- h. February 1943.
- i. May 1943.
- j. June 1943.
- k. July 1943.
- l. August 1943.
- m. September 1943.
- n. October 1943.
- o. November 1943.
- p. December 1943.
- q. January 1944.
- r. February 1944.
- s. March 1944
- t. September 1944.
- u. October 1944.
- v. November 1944.

85. Contract OEMsr-123, Washington University, C. F. Cori. Inf. Month. Prog. Rept. (NDRC B4-C), January 6, 1942.

86. Contract OEMsr-304, University of Chicago, M. S. Kharasch. Inf. Month. Prog. Rept. dated October 1943. Div. 9-255-M6

87. Contract OEMsr-556, New York University, H. W. Smith. Inf. Month. Prog. Rept. NDRC 9:5:1 No. 11, December 10, 1943. Div. 9-300-M1

88. Contract OEMemr-9, University of Pennsylvania, F. H. Adler.
- a. No. 20.
- b. No. 24, January 28, 1943.
- c. No. 27, April 2, 1943.
- d. No. 33, September 27, 1943.
- e. No. 42, April 28, 1944.

89. Contract OEMemr-24, Wilmer Institute, Johns Hopkins Hospital, A. C. Woods and J. S. Friedenwald.
- a. No. 10(?), June 25, 1942.
- b. No. 17, August 14, 1942.
- c. No. 18, August 18, 1942.
- d. No. 19, September 1, 1942.
- e. No. 26, December 4, 1942.
- f. No. 31, March 10, 1943.
- g. No. 35, May 4, 1943.
- h. No. 46, December 15, 1943 Div. 9-384-M3

90. Contract OEMemr-39, Yale University, Henry Bunting and M. C. Winternitz.
- a. No. 5, October 20, 1943.
- b. No. 6, October 20, 1943.
- c. No. 9, May 10, 1944.
- d. No. 10, May 10, 1944.

91. Contract OEMemr-57, University of Chicago, E. S. C. Barron. Div. 9-321.2-M1
- a. Report dated April 8, 1942.
- b. Report dated September 18, 1942.

92. Contract OEMemr-82, Johns Hopkins University, Maurice Sullivan, Report No. 7, dated November 25, 1942.

93. Contract OEMemr-90, Memorial Hospital, New York

City, C. P. Rhoads. Undated report entitled "The Toxic Effects of Arsine in Vivo and in Vitro, Their Prevention and Treatment." Div. 9-523-M1

94. Contract OEMemr-103, Cornell University Medical College, D. P. Barr and M. B. Salzberger.
    a. Report of April 20, 1942. Div. 9-315-M1
    b. No. B-22, April 15, 1944.
    c. No. B-26, June 20, 1944. Div. 9-302-M3
    d. No. B-28, July 31, 1944.
95. Contract OEMemr-141, Harvard University Medical School, D. G. Cogan. Report No. 22, dated January 7, 1944. Div. 9-382-M1
96. Contract OEMemr-245, Cornell University Medical College, McKeen Cattell. Report No. 8, dated February 7, 1944.
97. Contract OEMemr-253, Johns Hopkins University. W. T. Longcope.
    a. No. 1, February 1, 1943.
    b. Eagle Report No. 1, July 1, 1943.
    c. Eagle Report No. 2, October 18, 1943.
    d. Eagle Report No. 3, January 24, 1944.
98. Contract OEMemr-M-825, Memorial Hospital, New York City, C. P. Rhoads. (Later, Contract OEMemr-96)
    a. Report dated April 15, 1942.
    b. Report dated April 25, 1942.
    c. No. 6, August 31, 1942.
    d. No. 7, September 30, 1942.
    e. No. 9, November 30, 1942.
    f. No. 10, January 31, 1943. Div. 9-523-M1
    g. No. 11, March 31, 1943.

MISCELLANEOUS

99. *Collection of Papers on Chemical Warfare*, edited by Roger Adams, Joseph Dee, and W. C. Pierce, August 1, 1944. *IV. The Important Persistent and Non-Persistent War Gases*, by Homer W. Smith and John A. Zapp.
100. *Ibid.* — *I. The Gas Mask*, W. C. Pierce.
101. Contract OEMsr-97, Iowa State College, Henry Gilman. Correspondence dated:
    a. March 2, 1942.
    b. June 11, 1942.
    c. August 4, 1942.
    d. November 2, 1942.
102. Contract OEMsr-300, University of Illinois, R. C. Fuson. Correspondence dated April 28, 1943.
103. Contract OEMsr-394, University of Chicago, M. S. Kharasch. Correspondence dated:
    a. August 14, 1942.
    b. September 15, 1942.

UNITED STATES ARMY REPORTS

Chemical Warfare Service

104. EACD 92. *Report on Relation between Concentration and Limit of Tolerance for Diphenylaminechlorarsine and the Development of a Continuous Flow Apparatus for Testing*, January 25, 1922.
105. EACD 179. *Preparation of Allyldichlorarsine*, June 12, 1922
106. EACD 230. *The Laboratory Development of a Method for the Manufacture of M-1*, January 5, 1923.
107. EACD 257. *Preparation of Diphenylamine Cyanarsine*, March 16, 1923.
108. Supplement to EACD 257. *Preparation of Diphenylamine Cyanarsine*, April 21, 1928.
109. EACD 273. *Preparation of Phenyldifluorarsine*, July 20, 1923.
110. EACD 323. *Preparation of Dichlorarsanthrene*, September 18, 1924.
111. EACD 331. *Preparation of β-Chlorethyl Dichlorarsine*, February 3, 1925.
112. EACD 338. *Preparation of Ethyl Difluorarsine*, March 31, 1925.
113. EACD 346. *Preparation of β-Chlorvinyl Difluorarsine*, March 4, 1925.
114. EACD 440. *Attempted Preparation of Thio-bis-Ethyldichlorarsine*, December 7, 1927.
115. EAMRD 8 (Pts. 1 & 2). *The Toxicity, Pathology, Chemistry, Mode of Action, Penetration and Treatment for M-1 and Its Mixtures with Arsenic Trichloride*, August 13, 1923.
116. EAMRD 26. *Toxicity of Certain Compounds on Mice by Inhalation and Subcutaneous Injection. Vesicant and Lachrymatory Action on Man*, April 30, 1924.
117. EAMRD 36. *The Toxicity of Certain Arsenical Fluorides*, March 1, 1925.
118. EAMRD 91. *Effect of Humidity on the Vesicant Action of Mustard Gas, M-1, Methyldichlorarsine and Methyldifluorarsine*, June 25, 1928.
119. EATR 78. *Constants and Physiological Action of Chemical Warfare Agents*, July 19, 1932.
120. EATR 107. *The Effect of Hypercalcemic Agents upon Pulmonary Edema Induced by Phosgene*, September 20, 1932.
121. EATR 109. *Mouse Toxicity Data from January 1, 1933 to November 1, 1940 (Summary and Supplement 1)*, February 1, 1941.
122. EATR 214. *Lewisite (M-1), 1940 Summary of Data*, August 21, 1940.
123. EATR 230. *DM, Manufacture of 10,709 lb.*, March 8, 1937.
124. EATR 285. *Lewisite (M-1): 1940 Summary of Physiologic and Toxicologic Data*, March 15, 1941.
125. EATR 293. *Arsine as a Potential Chemical Warfare Agent, Summary of Available Data*, January 31, 1939.
126. EATR 320. *Mixture of Mustard Gas, Lewisite and Mineral Oil for Use as Airplane Spray*, February 28, 1940.
127. EATR 325. *Ethyl Dichlorarsine, Preliminary Investigation (1939)*, November 6, 1941.
128. EATR 335. *Lewisite (M-1): The Stereoisomers. Part I. Isolation and Identification. Part II. Physiologic Action: (1) Median Lethal Concentrations for Mice, (2) Skin Irritant Effects of the Vapors on Man, and (3) Median Detectable Concentrations*, April 25, 1941.
129. EATR 350. *Dichlorethylarsine (ED). Part I, Preparation; Destruction by RH-195 and C-1. Part II. Toxicity: Median Lethal Concentration for Mice. Part III. Median Detectable Concentration, Skin Irritant Action and Penetration of Impregnated Cloth*, August 28, 1942.
130. EATR 372. *Butyldichlorarsine. Part I. Preparation and*

Properties. Part II. Median Lethal Concentration for Mice, 10-min. Exposure; Skin Irritant Action on Rabbits and Penetration of Impregnated Cloths, June 3, 1942.

131. EATR 377. *Carodyl Chloride. Part I. Preparation and Properties. Part II. Median Lethal Concentration for Mice, 10-min. Exposure; Skin Irritant Action on Rabbits; Penetration of Impregnated Cloth*, October 17, 1942.

132. MD(EA) Memorandum Report No. 20. *Preliminary Experiments on the Toxicity of Arsine (AsH_3) to Rabbits by Inhalation*, January 15, 1942.

133. MD(EA) Memorandum Report No. 45. *The Use of 5 percent Hydrogen Peroxide in the First-aid Treatment of Liquid Lewisite Burns of Animals*, February 18, 1942.

134. MD(EA) Memorandum Report No. 60. *Effect of Urinary pH and Diet on Arsine Poisoning*, July 7, 1942.

135. MD(EA) Memorandum Report No. 61. *The Use of Hyperol (Urea-Hydrogen Peroxide, $CO(NH_2)_2 \cdot H_2O_2$) in the First-aid Treatment of Liquid Lewisite Burns of Rabbits.* Supplement to MD(EA) Memorandum Report 47, July 7, 1942.

136. MD(EA) Memorandum Report No. 70. *Toxicity of Chloroacetophenone (CN) and of Ethyldichloroarsine (ED) Contaminated Water to Rats*, October 17, 1942.

137 MD(EA) Memorandum Report No. 82. *Clinical and Laboratory Evidence of the Non-Toxic Effect of Lewisite Vesicle Fluid on the Skin*, March 12, 1943.

138. MRI(EA) 28. *The Therapeutic Effectiveness of BAL Solution against Liquid PD, ED and AsCl$_3$ in Eyes of Rabbits*, July 22, 1944.

139. TDMR 299. *M-1 Process Development. Mercuric Chloride Catalytic Process. Corrosion of Materials of Construction by Mercuric Chloride Catalyst Solution*, September 5, 1941.

140. TDMR 316. *New Compounds. Preparation of Carodyl*, November 3, 1941.

141. TDMR 323. *M-1 Process Development. Use of Mercuric Chloride Catalyst Solution in a Packed Tower Reactor*, November 12, 1941.

142. TDMR 326. *M-1 Process Development. Mercuric Chloride Catalytic Process. Corrosion Resistance of Miscellaneous Material to Mercuric Chloride Catalyst Solution and Crude M-1*, November 21, 1941.

143. TDMR 330. *M-1 Plant Design. Investigation of Certain Phases of Aluminum Chloride Process*, January 26, 1942.

144. TDMR 354. *M-1 Process Development. Pilot Plant Production of M-1 by a Continuous Process Using Mercuric Chloride Catalyst*, March 6, 1942.

145. TDMR 356. *New Compounds. Physical Constants of Certain Organic Compounds. A Memorandum Report*, June 20, 1942.

146. TDMR 374. *Median Lethal Concentration for Mice of a Mixture of 50% Mustard and 50% Lewisite*, May 16, 1942.

147. TDMR 376. *Variation in Catalyst Composition with Re-Use in the Mercuric Chloride Batch Process*, June 1, 1942.

148. TDMR 379. *Gas (J) for Navy HE Gas Projectile. Preparation of Carodyl in Experimental Plant*, May 26, 1942.

149. TDMR 380. *Phenyldichloroarsine. Median Lethal Concentration for Mice*, May 22, 1942.

150. TDMR 383. *Gas (J) for Navy HE Gas Projectiles. Preparation of Carodyl by Electrolytic Reduction of Cadet's Liquid*, June 10, 1942.

151. TDMR 387. *Carodyl Cyanide. Median Lethal Concentration for Mice; Skin Irritant Action*, June 2, 1942.

152. TDMR 392. *Carodyl Oxide. Median Lethal Concentration for Mice, 10-min. Exposure; Skin Irritant Action*, June 16, 1942.

153. TDMR 412. *M-1 Plant, Process Development. Methods of Analysis of Crude Lewisite and Lewisite Distillation Fractions*, July 28, 1942.

154. TDMR 419. *Process Development of M-1 Plant. Removal of Residual Tar from the M-1 Continuous Stripping Still*, August 9, 1942.

155. TDMR 424. *M-1 Plant Process Development. Conversion of Isomer 1 to Isomer 2*, August 16, 1942.

156. TDMR 445. *M-1 Plant Process Development. Estimation of Volatile Gases Dissolved in Crude M-1*, October 5, 1942.

157. TDMR 452. *Amyldichloroarsine and Isoamyldichloroarsine; Median Lethal Concentration for Mice; Vesicant Action on Man*, October 12, 1942.

158. TDMR 456. *Data on Chemical Warfare*, November 25, 1942.

159. TDMR 457. *A Mixture of 60% Lewisite, 40% Mustard. The Median Lethal Dosage by Skin Application*, October 20, 1942.

160. TDMR 461. *M-1 Plant, Process Development. Hydrochloric Acid Wash of Crude M-1*, November 12, 1942.

161. TDMR 466. *Wulff Process Development (Acetylene). Synthetic Mixtures in M-1 Production*, November 5, 1942.

162. TDMR 469. *M-1 Plant Process Development. Treatment of Plant M-1 for Reduction of Sludge Formation*. November 10, 1942

163. TDMR 473. *Lewisite; Dispersion as Airplane Chemical Spray*, November 20, 1942.

164. TDMR 474. *Freezing Tests of Vesicants in the M-30 Chemical Spray Tank*, November 25, 1942.

165. TDMR 476. *M-1 Plant, Process Development. Cuprous Chloride Process. A Search of the Chemical Literature for a Substance to Solubilize Cuprous Chloride*, November 30, 1942.

166. TDMR 499. *Storage of HS and M-1 in Concrete. Treatment of Concrete Tanks*, December 14, 1942.

167. TDMR 512. *The Comparative Vesicant Action of, and Penetration of Impregnated Cloth by, Mustard and Lewisite Airplane Spray Mixtures*, December 19, 1942.

168. TDMR 514. *Lewisite. Stability of Vapor of Lewisite and of Other Arsenicals toward Water Vapor*, January 6, 1943.

169. TDMR 515. *The Effect of Heat and Humidity on the Vesicant Action of Lewisite and Mustard*, December 24, 1942.

170. TDMR 517. *M-1 Plant Process Development. The Effect of $SiCl_4$ in AT Unit in Manufacturing M-1 by the $HgCl_2$ Batch Process*, January 7, 1943.

171. TDMR 518. *Corrosion of M47A1 Bombs*, January 1, 1943.

172. TDMR 525. *Methods of Analysis and Detection of Chemical Agents. Method for Field Sampling and Analysis of MS Vapors in Air*, January 14, 1943.

173. TDMR 533. *Persistent Vesicant Spray. Airplane Spray Tests with MSC, Thickened and Unthickened*, April 19, 1943.

174. TDMR 537. *New Compounds. Detonation Tests on*

Chloralkylamines Compared with HS, M-1 and ED, January 26, 1943.

175. TDMR 545. *Preparation of Lewisite (M-1): A Bibliography of References on Methods Other Than Aluminum Chloride Catalysis*, January 23, 1943.
176. TDMR 548. *Lewisite (M-1): The Stereoisomers. Investigation of Discrepancies between Nominal and Analytical Concentrations: Redetermination of LC_{50} for Mice*, January 29, 1943.
177. TDMR 550. *Freezing Tests of Vesicants on the Airplane Spray Tank M10*, February 20, 1943.
178. TDMR 551. *Arsine. Physiological Effects Resulting from Exposure to Sublethal Concentrations*, February 4, 1943.
179. TDMR 564. *Comparative Vesicant Action and Cloth Penetration of Mixtures of Various Compounds with Mustard and Lewisite*, February 19, 1943.
180. TDMR 568. *New Compounds: Preparation and Properties of β-Chlorovinyldifluorarsine*, April 20, 1943.
181. TDMR 582. *Sesquimustard and Sesquimustard Homologues. Vesicant Action and Cloth Penetration of Undiluted Compounds and Mixtures with Mustard and Lewisite*, March 15, 1943.
182. TDMR 592. *m-Nitrophenyldichlorarsine: LC_{50} for Mice: 10-min. Exposure*, March 13, 1943.
183. TDMR 601. *Vesicant Mixtures. Physical Constants of Mixtures of HS with Nitrogen Mustards and with ED*, March 26, 1943.
184. TDMR 604. *Bis(diphenylarsine) Oxide (DA Oxide), LC_{50} for Mice: 10-min. Exposure*, April 6, 1943.
185. TDMR 609. *M-1 Plant, Process Development, M-1 Production by the Solvent-batch Process with Cuprous Chloride-ethanolamine Hydrochloride as Catalyst*, April 9, 1943.
186. TDMR 615. *Median Detectable Concentrations by Odor of Plant Run Mustard, Plant Run Lewisite, and Pilot Plant Ethyl Nitrogen Mustard*, April 16, 1943.
187. TDMR 622. *M-1 Plant, Process Development, M-1 Production from Acetylene Made by the Regenerative Hydrocarbon Cracking Process*, April 16, 1943.
188. TDMR 625. *M-1 Plant, Process Development, M-1 Production by the Non-solvent Batch Process with Cuprous Chloride-ethanolamine Hydrochloride as Catalyst*, April 17, 1943.
189. TDMR 637. *β-Chlorovinyldifluorarsine. LC_{50} for Mice: Vesicant Action on Man*, April 28, 1943.
190. TDMR 639. *The Effect of Mustard and Lewisite on the Colloidal Gold Curve of Spinal Fluid*, May 4, 1943.
191. TDMR 648. *Distribution and Rate of Penetration of Lewisite in Skin*, May 1, 1943.
192. TDMR 670. *M-1 Plant, Process Development. Sludge Reduction in Crude M-1 by Hydrochloric Acid Phosgene Wash*, June 2, 1943.
193. TDMR 671. *The Effect of Several Chemical Warfare Agents on the Kratschmer's Reflex in Rabbits*, June 10, 1943.
194. TDMR 688. *A Mixture of Mustard (HS) and Dichlorethylarsine (ED) 50-50 by Weight: LC_{50} for Mice*, June 17, 1943.
195. TDMR 691. *Derivatives of Chemical Warfare Agents. Toxicity Study No. 1*, June 25, 1943.
196. TDMR 702. *M-1 Plant, Process Development: Test for Use in the M-1 Process of 17 Made from Low-grade Arsenic Ores*, July 16, 1943.
197. TDMR 707. *L Plant, Process Development. Test of Suitability of Arsenic Trichloride Sample GRS-429-48*, July 23, 1943.
198. TDMR 716. *Cuprous Chloride L Process*, August 10, 1943.
199. TDMR 730. *A Preliminary Study of the Effect of Wetting Agents on the Vesicant Power of H and L*, August 30, 1943.
200. TDMR 733. *Development of L Pilot Plant. Cuprous Chloride Process and Hydrochloric Acid-Phosgene Treatment*, August 31, 1943.
201. TDMR 739. *$AsCl_3$ Plant, Process Development. Corrosion of Iron Caused by Moisture in the AO Used*, September 22, 1943.
202. TDMR 760. *Methods of Analysis of Antimony in Arsenical Liquors*, November 1, 1943.
203. TDMR 761. *Methods of Analysis of L Prepared by the Cuprous Chloride and Mercuric Chloride Processes*, November 1, 1943.
204. TDMR 762. *Regenerative Hydrocarbon Cracking Process. Test of Acetylene Produced in L Production by Cuprous Chloride Batch Process*, November 3, 1943.
205. TDMR 777. *Antimony Trichloride as an Accelerator for Production of L by the Mercuric Chloride Process*, December 1, 1943.
206. TDMR 794. *Purification of Carbide Acetylene by Countercurrent Scrubbing in a Packed Tower*, January 19, 1944.
207. TDMR 804. *Vapor Pressure Curves of Agents and Solvents*, February 26, 1944.
208. TDMR 1031. *Corrosion by Vesicants: Rate of Corrosion of Steel and Other Metals by H, HQ, HN3, HN1, and L, Mostly at 65° C*, April 2, 1945.
209. TRLR 1. *Lewisite. Determination of Vesicant Action on Man by Use of a Continuous Flow Chamber*, August 21, 1943.
210. TRLR 2. *Studies of the Mechanism of the Physiological Action of Mustard Gas. Part II. The Effect of Organic Arsenicals*, September 13, 1943.
211. TRLR 3. *m-Nitrophenyldichlorarsine. LC_{50} for Mice on 10-minute Exposure*, September 10, 1943.
212. TRLR 8. *Lewisite-Lewisite Oxide: Vesicant Action*, October 13, 1943.
213. TRLR 16. *Ethyldichlorarsine (ED). Explosion Test in the M70 Airplane Bomb*, December 15, 1943.
214. TRLR 18. *L, HN-1, H and HQ. Effects of 0.1-mg Drops on Eyes of Rabbits*, December 20, 1943.
215. TRLR 24. *The Rate of Liberation of H and L from Some Calcareous Soils. A Preliminary Report*, March 25, 1944.
216. CWS Field Laboratory Memorandum 1-4-5. *Medical Division Status Summaries*, August 1944.
217. Medical Research Laboratory Informal Monthly Progress Report, August 15, 1943.

MISCELLANEOUS

218. Technical Manual 8-285. *Treatment of Casualties from Chemical Agents*, U. S. War Department, April 15, 1944.

UNITED STATES NAVY REPORTS

Naval Research Laboratory

219. P-2304. *A Controlled Laboratory Experiment to Compare Lesions Resulting from Application of Mustard, Lewisite and Nitrogen Mustards to the Skin of the Forearms of Humans*, September 1, 1944.

220. P-2483. *Chamber Tests with Human Subjects. VI. Arm Chamber Exposures to L Vapor*, May 31, 1945.

MISCELLANEOUS UNITED STATES REPORTS

221. BCWR 1717. *Notes on Visits to Huntsville and Pine Bluff Arsenals, July 26-31, 1943*, by L. T. D. Williams, August 7, 1943.

222. BCWR 2077. *Notes on a Meeting of Plant Medical Officers, Safety Engineers, and Medical Consultants at Huntsville Arsenal, Alabama, September 15-16, 1943*, by L. T. D. Williams.

223. BCWR 2380. *Second Conference of Medical Officers and Consultants, Held at Pine Bluff Arsenal, Arkansas, 16-17 November, 1943*, by L. T. D. Williams.

224. Ph. 237. *Mustard-1, Chemical, Pathological and Toxicological Characteristics. Physiological Action and Comparisons with Other Substances*, J. A. E. Eyster.

225. AM 538. *The Relative Military Value of Mustard-1 and G-34*, J. A. E. Eyster and A. S. Loevenhart.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

226. Porton Memorandum No. 10A. *The Chemical Contamination of Water Supplies*, May 26, 1941.

227. Porton Memorandum No. 15. *Classified List of Compounds Examined Physiologically Since 1919*, October 1941.

228. Porton Memorandum No. 28. *Methods of Decontamination*, April 15, 1941.

229. Porton Report No. 1248. *The Effects of the Relative Humidity and Temperature of the Air on the Vesicant Power of Drops of Lewisite When Falling through the Atmosphere*, June 18, 1934.

230. Porton Report No. 1334. *Report on the Effects of Temperature and Relative Humidity on the Rate of Evaporation of Drops of Lewisite Suspended in Air Streams of Various Velocities*, April 17, 1935.

231. Porton Report No. 1537. *Report on the Physiological Examination of Certain Substituted Arsines*, May 25, 1936.

232. Porton Report No. 2026. *Interim Report on the Rate of Evaporation of Drops of a Mixture of Mustard Gas and Lewisite*, October 25, 1936.

233. Porton Report No. 2115A. *Preliminary Report on the Suitability of Various Charges. Part I. Aircraft Spray*, August 26, 1939.

234. Porton Report No. 2150. *Lewisite Shock*, December 21, 1940.

235. Porton Report No. 2165A. *The Toxicity of Lewisite II and Lewisite II Oxide*, February 14, 1941.

236. Porton Report No. 2172. *The Offensive Use of Arsine*, February 6, 1941.

237. Porton Report No. 2176. *Pathological Changes Produced in Small Laboratory Animals by Arsenic Trichloride and Phenyl Dichloroarsine, with a Note on Treatment*, March 6, 1941.

238. Porton Report No. 2183. *Pathology of Lewisite Poisoning by Laboratory Animals. Third Report*, February 21, 1941.

239. Porton Report No. 2201. *Assessment of Danger of Systemic Poisoning by Lewisite*, April 29, 1941.

240. Porton Report No. 2203. *Fourth Report on Lewisite Poisoning. Pathology and Treatment*, May 24, 1941.

241. Porton Report No. 2246. *Systemic Effects Induced by Mustard Gas Poisoning. First Report*, July 30, 1941.

242. Porton Report No. 2249. *Treatment of Lewisite Skin Contamination by Wet Dressings of 3% H_2O_2 or 10% Hyperol, and its Comparison with D.T.H. Treatment*, August 5, 1941.

243. Porton Report No. 2258. *The Physiological Action of Arsine*, August 12, 1941.

244. Porton Report No. 2272. *Physical Constants of Arsenicals Related to D.C.*, September 10, 1941.

245. Porton Report No. 2275. *Fourth Report on Arsine Poisoning*, September 12, 1941.

246. Porton Report No. 2306. *Trial with Shell Charged D.C. Mk. I Functioned at Rest*, December 2, 1941.

247. Porton Report No. 2321. *The Effect of Repeated Short Periods of Exposure to High Concentrations of D.C.*, February 5, 1942.

248. Porton Report No. 2341. *The Use of the 65-lb. Bomb for the Attack of Tanks*, February 11, 1942.

249. Porton Report No. 2347. *Systemic Effects Following Skin Application of Diphenylchloroarsine (DA)*, March 25, 1942.

250. Porton Report No. 2388. *Preliminary Report on the Effect of Terrain on the Evolution of Vapour from Lewisite*, July 18, 1942.

251. Porton Report No. 2400. *The Use of an Assault Course in the Assessment of the Arsenical Smokes*, August 18, 1942.

252. Porton Report No. 2420. *Toxicity of Phenyldibromarsine, Phenyldiiodoarsine and Phenyldifluoroarsine*, September 10, 1942.

253. Porton Report No. 2486. *Effectiveness of S.A.A. (Non-Armour Piercing) Charged with CW Agent against Crews of A.F.V.'s*, February 28, 1943.

254. Porton Report No. 2493. *The Physiological Effects of Various Substances on the Rabbit's Eye: A Preliminary Survey of Chemical Eye Injurants with Particular Reference to Molecular Structure and CW Potentialities*, March 7, 1943.

255. Porton Report No. 2508. *Lymph Drainage in Lewisite Poisoning*, June 2, 1943.

256. Porton Report No. 2518. *The Prevention of Vesication*, July 20, 1943.

257. Porton Report No. 2542. *Nature of Air-borne Lewisite*, October 11, 1943.

258. Porton Report No. 2553. *The Effect of Lewisite Vapor on Small Animals and on Man*, October 20, 1943.

259. Porton Report No. 2560. *Some Further Studies on the Treatment of Mustard Gas Blisters and a Comparison of the Healing of Mustard Gas and Lewisite Burns*, November 10, 1943.
260. Porton Report No. 2583. *Treatment of Eye Lesions Produced by Mixtures of Mustard Gas and Lewisite*, January 17, 1944.
261. Porton Report No. 2624. *The Treatment of Lewisite Shock with Sodium Salt Solutions*, June 6, 1944.
262. Porton Report No. 2655. *Storage Trials. Bombs A.C., L.C., 65-lb. Charged Vesicants*, November 23, 1944.
263. Porton Report No. 2665. *Notes on the Permeability of Systemic Capillaries Following Intra-Arterial Injection of Lewisite Oxide*, February 1, 1945.
264. Porton Report No. 2678. *The Toxicity and Therapeutic Value of BAL and BAL-Intrav. Part I*, May 21, 1945.
265. Porton Report No. 2679. *The Effect of BAL upon Excretion of Arsenic in the Bile of Dogs and Rabbits*, May 29, 1945.
266. Porton Departmental Report No. 76. *Report on the Skin Burning Power of Various Vesicant Mixtures through Service Dress*, July 22, 1939.
267. Porton Departmental Report No. 206. *Preparation and Properties of Mixed Furyl (β-chlorovinyl) arsines*, June 24, 1940.
268. Ptn 983(R.13831). *Estimation of Arsenic Compounds in Blood*, April 20, 1942.
269. Ptn.1150(R.10244). *Report on the Physiological Examination of m-Acetyldiphenyl Chloroarsine, Diphenyl Thiocyanoarsine, m-Acetyldiphenylcyanoarsine, m-Chloroacetyl Diphenylcyanoarsine, m-Chloroacetyl Diphenylchloroarsine*, August 25, 1941.
270. Ptn.1161(R.12902). *Experiments to Establish the Effects of DC on the Eyes of Rabbits*, October 27, 1941.
271. Ptn.1180(R.14040). *Report on the Physiological Examination of Phenyl Difluoro-Arsine*, December 12, 1941.
272. Ptn.1234(R.8007). *The Treatment of Lewisite Poisoning with Intravenous Injections of Methylene Blue, Potassium Permanganate and Sodium Thiosulphate*, July 22, 1941.
273. Ptn.2104 6(R.1056). *Physiological Examination of 4:4'Dichlorodiphenyl Chloroarsine and 4:4'Dichlorodiphenyl Cyanoarsine*, January 14, 1941.
274. Ptn.2104 6(R.1057). *Report on the Physiological Examination of Six DC Analogues*, January 14, 1941.
275. Ptn.2104 6(R.11234). *Report on the Physiological Examination of Chlorohydroxyphenylarsine o-Carboxylic Lactone*, September 12, 1941.
276. Ptn.2801 3(8.9102). *Effects of Small Droplets of Lewisite on the Eyes of Rabbits*, July 11, 1942.
277. Ptn.2820(T.9300A). *Comparison of the Effects of H and Lewisite on Living Tissues*, July 10, 1943.
278. Ptn.3200(8.2856). *Comparison of T.65%, DC and C.A.P. as Chargings in S..1..1. for Attack on A.F.V.'s*, March 3, 1942.
279. Ptn.3850(T.15070). *Contamination of Water Supplies. Special Water Contaminants.*
280. Ptn.4000(T.5415). *Tabular Summary of Properties, Protection, etc., and Consideration as Alternate Chargings in A/C Weapons (Bombs and Spray) of Chemical Warfare Agents*, April 29, 1943.
281. Ptn.4280(8.1871). *Report on the Physiological Examination of Diphenyl Fluoroarsine and Dimethyl Fluoroarsine*, January 7, 1942.
282. Ptn.4280(8.1675). *Comments from Porton on Dr. A. Sporzynski's Report on Experiments Carried Out in Poland with Phenyldifluoroarsine*, April 1942.
283. Ptn.4300(8.2177). *Physiological Examination of 4:4'thio-(Dichloroarsine) Diphenyl Disulphide and 3-β-Chloroethylthiophenyldichloroarsine*, February 16, 1942
284. Ptn.4300(T.13031A). *An American Histochemical Test for Lewisite*, October 5, 1943.
285. C.D. Report No. 1091. *Report on the Physiological Examination of Certain Arsenicidine Analogues*, March 19, 1942.

Research Establishment, Sutton Oak

286. Production of Lewisite
a. S.O. R 448. *Production of Lewisite by a New Process. Part I*, December 13, 1939.
b. S.O. R 466. *The Production of Lewisite by a New Process. Part III. The Physical Properties of Arsenic Trichloride and the Lewisites*, July 4, 1940.
c. S.O./R/507. *Production of Lewisite by the Mercuric Chloride Process. Part V. Operation of a 1 Ton/Week Crude Lewisite Stripping Unit*, February 25, 1941.
d. S.O. R 528. *The Production of Lewisite. Part VI Exploratory Work on the Production of Lewisite in the Vapour Phase*, April 28, 1941.
e. S.O. R 531. *The Production of Lewisite. Part VII. Possible Alternative Processes*, May 27, 1941.
f. S.O. R 549. *The Production of Lewisite. Part VIII. Laboratory Development of the Cuprous Chloride Process*, August 26, 1941.
g. S.O. R 565. *The Production of Lewisite. Part IX. Semi-Technical Development of the Cuprous Chloride Process*, January 6, 1942.
h. S.O. R 610. *The Production of Lewisite. Part X. Operation of a Plant Designed to Produce 10 Tons/Week Stripped Lewisite by the Mercuric Chloride Process*, August 24, 1942.
i. S.O. R 648. *Production of Lewisite. Part XI. Operation of a 10 Ton per Week Pilot Plant for the Production of Lewisite by the Cuprous Chloride Process*, March 5, 1943.
j. S.O. R 697. *Production of Lewisite. Part XII. Operation of a 10 Ton Week Pilot Plant for the Production of Lewisite by the Cuprous Chloride Process*, January 6, 1944.

287. Iso-Lewisite
a. S.O. R 650. *Iso-Lewisite. Part I. Preparation and Properties of Iso-Lewisite*, April 20, 1943.
b. S.O. R 660. *Iso-Lewisite. Part II. The Structure of Lewisite and Iso-Lewisite*, April 10, 1943.
c. S.O. R 667. *Iso-Lewisite. Part III. Physicochemical Properties of Iso-Lewisite*, May 31, 1943.

288. Phenoxarsine Oxide
a. S.O. R 655. *Phenoxarsine Oxide. Part I. Improved Laboratory Scale Preparation*, May 1, 1943.
b. S.O. R 690. *Phenoxarsine Oxide. Part II. Semi-Scale Preparation*, January 11, 1944.

289. Physico-Chemical Studies on the Pope-Turner Reaction
a. S.O. R 592. *Physico-Chemical Studies on the Pope-Turner Reaction. Part I. The Decomposition of Phenylarsenious Oxide (MAO)*, February 6, 1942.
b. S.O. R 612. *Physico-Chemical Studies on the Pope-Turner Reaction. Part II. The Decomposition of Phenyldichlorarsine (MA)*, August 17, 1942.
c. S.O. R 613. *Physico-Chemical Studies on the Pope-Turner Reaction. Part III A Physico-Chemical Method of Analysis*, August 17, 1942.
d. S.O. R 619. *Physico-Chemical Studies on the Pope-Turner Reaction. Part IV. The Interaction of MAO and MA*, October 12, 1942.
e. S.O. R 695. *Physico-Chemical Studies on the Pope-Turner Reaction. Part V. Equilibria*, December 31, 1943.

290. Diphenylcyanoarsine
a. S.O. R 515. *Diphenylcyanoarsine. Statement on Efficiencies and Raw Material Requirements on the Pope-Turner Process to D.C.*, May 21, 1941.
b. S.O. R 516. *Diphenylcyanoarsine. Part XV. The Preparation of Diphenylcyanoarsine from Diphenylchloroarsine via Pope-Turner and Double Dimutization*, May 28, 1941.
c. S.O. R 517. *Diphenylcyanoarsine. Part XVI. The Continuous Distillation of Unstripped Pope-Turner D.A.*, July 14, 1941.
d. S.O. R 522. *Brief Summaries of Processes Used at Research Establishment, Sutton Oak*, June 11, 1941.
e. S.O. R 523. *The Production of Low-Melting-Point Vesicants. Part I. Preliminary Survey of Possible Methods*, March 31, 1941.
f. S.O. R 559. *Preparation of DM-DC Complex with Low Vapour-Pressure*, November 24, 1941
g. S.O. R 561. *The Vapour Pressure of Arsenious Chloride and of Lewisite I*, December 5, 1941.
h. S.O. R 564. *Diphenylcyanoarsine. Part XVII. Further investigation of the Pope-Turner Condensation*, January 5, 1942.
i. S.O. R 570. *The Vapour-Liquid Equilibria of the Lewisite 1-2-Trichlorethane System*, February 4, 1942.
j. S.O. R 574. *Methyl Dichloroarsine. Part I. Laboratory and Semi-Scale Preparation*, March 4, 1942.
k. S.O. R 580. *The Recovery of Arsenious Oxide from the Condensation Stage of the Pope-Turner Process and the Manufacture of Sodium Arsenite*, March 28, 1942.
l. S.O. R 583. *Diphenylcyanoarsine. Part XVIII. The Preparation of 3:1 Mixed Oils for the Pope-Turner Condensation*, April 3, 1942.
m. S.O. R 586. *Diphenylcyanoarsine. Part XIX. The Preparation of 3:1 Mixed Oils (Direct Method) in Semi-Technical and Production Units*, April 2, 1942.
n. S.O. R 589. *Diphenylcyanoarsine. Part XX. The Conversion of 3:1 Mixed Oils to D.A in Semi-Technical and Production Units*, April 3, 1942.
o. S.O. R 590. *The Diffusion of 2-Chlorovinyldichloroarsine (Lewisite I) in Still Air*, August 17, 1942.
p. S.O./R/600. *The Polarisability of the Arsenic Atom*, May 30, 1942.
q. S.O. R 622. *Part XXI. Report of a Production Run for Manufacturing D.A from Phenylarsonic Acid Using the Modified Pope-Turner Process*, October 16, 1942.
r. S.O./R 706. *N-Methyl-2,2'-dichlorethylamine (S). Part XII. The Life-Time of Spherical Drops of S in Still Air at 25° C and 1 Atm. Pressure*, February 21, 1944.
s. S.O./DES/585. *Plant for the Production of 10 Tons per Week of Stripped Lewisite by the Cuprous Chloride Process*, April 2, 1942.
t. S.O./DES/596. *Diphenylcyanoarsine. Part XXI. Design Memorandum for the Manufacture of 18.5 Tons of 91 Per Cent DA or 17.5 Tons of 90 Per Cent DC by the Modified Pope-Turner Process*, June 15, 1942.

Extramural Research

291. Cambridge Extramural Testing Station (E. D. Adrian)
a. XZ.20 (V.21355(A)). *Statement on the Eighth Month's Work*, by H. McCombie, B. A. Kilby, M. Thacker, February 5, 1941.
b. XZ.41 (V.21355(C)). *A Comparison of the Toxicities by Inhalation of p-Dimethylaminophenyl Arsenious Oxide and MA Oxide*, by McCombie, Kilby, Thacker, February 6, 1941.
c. XZ.76 (V.15453(B)). *The Physiological Examination of 3-Methyl-5-Chloro-5:10-Dihydroarsacridine* by McCombie, Kilby, Thacker, November 5, 1941.
d. XZ.80 (V.15453(E)). *Physiological Examination of 5-Cyano-5:10-Dihydroarsacridine*, by H. McCombie, B. C. Saunders, M. Kilby and B. A. Kilby, November 12, 1941.
e. XZ.83 (V.19437). *Physiological Examination of Two Arsacridine Derivatives*, by H. McCombie, B. A. Kilby, M. Kilby and B. C. Saunders, December 22, 1941.
f. XZ.86. *Physiological Examination of 2-Methyl-5-cyano-5:10-Dihydroarsacridine*, by H. McCombie, B. A. Kilby, M. Kilby and B. C. Saunders, February 2, 1942.
g. XZ.87. *Physiological Examination of Two Arsenical Sternutators*, by H. McCombie, B. A. Kilby, M. Kilby and B. C. Saunders, February 2, 1942.

292. Cambridge Biochemical Laboratory (M. Dixon)
a. Rept. No. 8 (V.10348). *Studies on the Mechanism of Blister Formation*, by F. D. Danielli and M. Danielli, September 8, 1941.
b. Rept. No. 20 (V.8855). *Interim Report on the Study of Capillary Permeability to Protein in Lewisite Poisoning*, July 23, 1943.
c. Rept. No. 24 (V.20194). *A Study of the Local Lesion Following the Application of Lewisite to the Skin, and of the Action of Lewisite on Skin Nuclear Phosphatase*, by J. F. Danielli, February 2, 1944.
d. Rept. No. 26 (Z.1576). *BAL-Intox: A New Non-Toxic Thiol for Intravenous Injection in Arsenical Poisoning*, by J. F. Danielli, M. Danielli, P. D.

Mitchell; L. N. Owen and G. Shaw, April 21, 1944.

293. Cambridge University — Strangeways Research Laboratory (H. B. Fell)
   a. (U.22947). *Report on the Effect of Lewisite and Lewisite Oxide on Living Cells in Vitro*, by H. B. Fell and C. B. Allsopp, February 1941.
   b. (V.15658). *Report on the Effect of a Dithiol Compound (DTH) on Tissue Cultures Grown in Medium Containing Lewisite Oxide*, by H. B. Fell and C. B. Allsopp, November 1941.

294. Cambridge University - Molteno Institute (D. Keilin)
   a. (V.13818). *Effects of Arsine on Blood, Metabolism and Enzymes*, by D. Keilin and E. F. Hartree, October 28, 1941.
   b. (W.2164). *Effect of Arsine on Haemoglobin: Formation of Bile Pigments*, by D. Keilin and E. F. Hartree, May 5, 1942.

295. Cambridge University (D. G. Cordier)
   a. (V.3204). *Absorption through the Skin and Systemic Effects of Mustard Gas and Lewisite*, by D. G. Cordier, May 19, 1941.
   b. (W.6691). *Modifications of the Volumes of the Tidal Air, Dead Space and Lungs during the Evolution of Subacute Pulmonary Oedema Caused by Lewisite*, July 17, 1942.

296. Imperial College of Science and Technology (H. V. A. Briscoe)
   a. (U.356). *Additional Observations on Physical Properties of Arsine*, by H. V. A. Briscoe and H. G. Emeleus, January 6, 1940-March 15, 1940.
   b. (U.11659). *The Physical Properties and Stability of Arsine*, by H. V. A. Briscoe and H. G. Emeleus, August 23, 1940.
   c. (Z.7186). *The Difluoroarsines*, by L. H. Long, August 8, 1944.

297. Imperial College of Science and Technology (I. M. Heilbron)
   a. (U.23062). *Fifth Report on Lacrimators and Vesicants Containing Nitrogen and or Halogen*, by I. M. Heilbron, D. H. Hey, E. R. H. Jones, D. F. Elliott and J. R. Catch, February 25, 1941.

298. Imperial College, London
   a. C.D. Report 1076. *Chemical, Physical and Physiological Properties of Certain Volatile Fluorine Compounds*, by A. L. G. Rees, March 3, 1941.

299. Nuffield Laboratory of Ophthalmology, Oxford Eye Hospital (I. Mann)
   a. (V.15621). *Further Interim Report on the Result of Treatment of Lewisite Lesions of the Rabbit's Eye with Dithiol*, by Ida Mann, A. Pirie and B. D. Pullinger, November 24, 1941.
   b. (V.16314). *Report on the Effect of Ethyldichlorarsine (Dick) on the Eye of the Rabbit and Treatment of the Resultant Injury with D.T.H.*, by Ida Mann and A. Pirie, January 21, 1942.
   c. (V.23247-A) *Report on the Effect of Methyl Dichlorarsine (Methyl Dick) on the Eye of the Rabbit and Treatment of the Resultant Injury with D.T.H.*, by Ida Mann and A. Pirie, March 18, 1942.
   d. (W.2354). *The Clinical Course of Lewisite Lesions of the Rabbit's Eye*, by Ida Mann, A. Pirie and B. D. Pullinger, May 8, 1942.
   e. (W.9282). *Interim Report on the Action of DTH Applied to the Outsides of the Closed Lids of a Rabbit's Eye after Injury by a Splash of Liquid Lewisite in the Unanaesthetized Rabbit*, by Ida Mann and A. Pirie.
   f. (W.14125). *Effect of Liquid DTH Rubbed on the Skin of the Lids Avoiding the Lid Margin after a Liquid Lewisite Lesion*, by Ida Mann and A. Pirie, November 1942.
   g. (W.14758(A)). *Action of DTH Applied to the Outsides of Closed Eyelids after Lewisite Injury*, by Ida Mann and A. Pirie.

300. Oxford Biochemical Laboratory (R. A. Peters)
   a. Report No. 4 (U.2226). *An Analysis of the Action of Arsenic and Arsenical Vesicants on Carbohydrate Oxidation*, by H. M. Sinclair and R. H. S. Thompson, May 7, 1940.
   b. Report No. 12. *Progress Report upon Specificity of Poisoning of Various Enzyme Systems by Certain Vesicating Agents or Skin Irritants. Oxidase Systems*, by R. A. Peters and R. W. Wakelin, August 12, 1940.
   c. Report No. 20. *Arsenic Derivatives of Thiol Proteins*, by L. A. Stocken and R. H. S. Thompson, December 2, 1940.
   d. Report No. 22. *Progress Report upon Investigations with Arsenical Substances*, by R. A. Peters, December 1940.
   e. Report No. 27. *An Analysis of the Action of Arsenite upon the Oxidation of Pyruvate*, by H. M. Sinclair, December 1940.
   f. Report No. 33. *The Treatment of Arsenical Burns with Dithiol Compounds*, by L. A. Stocken and R. H. S. Thompson, April 26, 1941.
   g. Report No. 43 (V.15200). *On the Amount of Mustard Entering the Skin from Saturated Vapor at 30°*, by A. C. Ogston, November 1941.
   h. Report No. 52 (V.20711). *The Chemistry and Toxicity of Thiols and Thioarsenites and the Significance of Thioarsenite Formation in the Treatment of Early Arsenical Burns*, by L. A. Stocken, R. H. S. Thompson, and V. P. Whittaker, February 9, 1942.
   i. Report No. 64 (W.18875). *Further Report on the Chemistry and Therapeutic Value of Dithiols in Arsenical Poisoning*, by L. A. Stocken and R. H. S. Thompson, January 22, 1943.
   j. Report No. 69 (Y.2305). *The Biochemical Basis of the Pathology and Therapy of Arsenical Poisoning (A Review)*, by R. A. Peters, L. A. Stocken, R. H. S. Thompson, and V. P. Whittaker, March 23, 1943.
   k. Report No. 70. *Lethal Contamination of Rats with Lewisite Treated with DTH Ointment*, by R. H. S. Thompson, March 24, 1943.
   l. Report No. 73 (Y.7735). *Oral Administration of DTH to Man and Animals*, by L. A. Stocken and R. H. S. Thompson, June 18, 1943.
   m. Report No. 74 (Y.10360). *The Value of ω-Dithiols*

in Arsenical Therapy, by V. P. Whittaker, July 1943.

n. Report No. 83. *Preparation and Pharmacological Properties of Mapharside-BAL Compound*, by R. A. Peters and L. A. Stocken, February 1945.

o. (V.2402). *The Effect of Arsenite and Arsenical Vesicants on the Respiration of Skin*, by R. H. S. Thompson, April 30, 1940.

p. (V.15450). *Thiol and Arsenic Metabolism after DTH Treatment of Lewisite Burns*, by R. H. S. Thompson and L. A. Stocken, November 12, 1941.

q. (V.21890). *The Antidotal Activity of B.A.L. against Therapeutic Arsenicals*, by L. A. Stocken, R. H. S. Thompson, and V. P. Whittaker, February 1944.

r. (Z.11030). *The Treatment of Complication of Arsenic-Therapy with a New Antidote, OX.217, Otherwise Known as BAL. Interim Report*, by A. B. Carleton, R. A. Peters, L. A. Stocken, R. H. S. Thompson, and D. I. Williams, October 19, 1944.

301. Oxford University – Dyson Perrins Laboratory (R. Robinson)

a. (U.2207). *Note on the Preparation of Furyl Dichloroarsine, Difuryl Chloro-arsine and Trifuryl Arsine*, by L. J. Goldsworthy and R. Robinson, April 27, 1940.

b. Report No. 62 (V.8173). *Diphenylchloroarsine-3-carboxylic Acid, Methyl Diphenylchloroarsine-3-carboxylate, Methyl Diphenylcyanoarsine-3-carboxylate, Diphenylchloroarsine-4-carboxylic Acid, Methyl Diphenylchloroarsine-4-carboxylate, Methyl Diphenylcyanoarsine-4-carboxylate*, by J. A. John, S. G. P. Plant, and R. Robinson, July 26, 1941.

c. Report No. 112 (V.16049). *γ-Chloroallyldichloroarsine (T.2008)*, by A. F. Childs, S. G. P. Plant, and R. Robinson, October 27, 1943.

d. W-131-5, A. *Note on Preparation of Trifuryl Arsine*, by R. Robinson, April 27, 1940.

e. W-131-5, B. *Summary of Second 6-Monthly Report* (October 1940) by R. Robinson.

f. Ptn 1165(R.6658). *Report on the Physiological Examination of 3,4,4'-Trimethyl diphenylcyanoarsine 2,4',4-Trimethyl diphenylcyanoarsine*, by R. Robinson, May 29, 1941 (W.A-11-31).

g. Ptn.1165(R.7849). *Report on the Physiological Examination of Di-α-naphthyl cyanoarsine*, by R. Robinson, June 26, 1941 (W.A-11-40) (V.5747).

h. Ptn.1165(R.12491). *Physiological Examination of Some Analogues of DA and DC*, by R. Robinson, October 20, 1941 (W-40-26).

i. *Second Report on Extramural Investigations at the Dyson Perrins Laboratory. Summary of Second 6-Monthly Report Part I. Arsenic Derivatives of Thiophene and Furan. Part II. Substituted Diarylcyanoarsines. Part III. Miscellaneous Investigations. Part IV. Preparation of Organic Arsenic Chlorides*, October 1940.

j. (V.15004). *Part I. Substituted Diarylcyanoarsines and Related Compounds. Part II. An Investigation of the Preparation of ω-Chloroacetophenone. Part III. Miscellaneous Preparations. Part IV. The Preparation of Organic Arsenic Chlorides. Part V. The Preparation of Some Local Anaesthetics*, October 31, 1941.

302. Rothamsted Experimental Station

a. (U.21432). *Discussion of Results and Summary of Work Carried Out on the Effect of Mustard and Lewisite Spray on Agricultural Crops*, by C. J. Russell and D. J. Watson, February 6, 1941.

303. University College, Southampton (N. K. Adam)

a. (V.17397). *Vapour Pressure of C. W. Agents*, by E. W. Baker, December 1941.

b. (V.22233). *Vapour Pressure of C. W. Agents*, by E. W. Baker and N. K. Adam, February 1942.

c. (V.24372). *Vapour Pressure of C. W. Agents*, by E. W. Baker and N. K. Adam, March 31, 1942.

d. (Z.3650). *Determination of Vapour Pressures Down to 10^{-4} mm. of Mercury with an Effusion Manometer. Vapour Pressures of CAP, D.C. and DDT*, by E. W. Baker, May 24, 1944.

304. University of Edinburgh (G. F. Marrian)

a. (U.19509). *Interim Report on Arsine Poisoning*, by G. F. Marrian, G. A. Levvy, and Assistants, January 1941.

b. (V.9005). *The Effect of Ethane-1:2-dithiol on Arsine-poisoned Mice*, by G. A. Levvy, June 1941.

c. (V.20288). *The Specific Toxic Action of Arsine on Tissues*, by G. A. Levvy and William Hughes, February 4, 1942.

d. (V.18483). *A Study of the Action of Arsine on Solutions of Crystalline Horse Haemoglobin*, by A. F. Graham, G. F. Marrian, and T. B. B. Crawford, December 11, 1941.

e. (V.22003). *The Chemical Nature of the Non-dialysable Arsenic Formed in Blood by the Action of Arsine*, by A. F. Graham, T. B. B. Crawford, and G. F. Marrian, February 28, 1942.

f. (V.22002). *The Toxicity of Arsine for Mice*, by G. A. Levvy, March 3, 1942.

g. (W.1429). *The Fixation of Arsine by the Tissues*, by G. A. Levvy, April 1, 1942.

h. (W.3520). *Further Observations on the Action of Arsine on Haemoglobin*, by A. F. Graham and G. F. Marrian, May 1942.

305. University of Edinburgh (J. M. Robson)

a. (V.18171). *Experiments on the Action of Toxic Gases on Drosophila Melanogaster*, by C. Auerbach, M. Y. Ansari, and J. M. Robson, December 23, 1943.

306. University of Edinburgh (G. A. Levvy)

a. (V.6003). *The Arsenic Contents of Rabbit Tissues, Urine and Faeces Following the Application of Phenyldichloroarsine (M.A.) to the Skin*, by I. D. E. Storey, May 15, 1943.

b. (V.14520). *Histopathological Changes in Rabbits after Contamination with Phenyldichloroarsine*, by J. Dekanski, October 28, 1943.

c. (V.6002). *Disappearance of Arsenic from the Contaminated Area Following Treatment of Rabbits with Phenyldichloroarsine (M.A.)*, by A. F. Graham and G. A. Levvy, June 5, 1943.

d. (V.18154). *Disappearance of Arsenic from the Contaminated Area Following Treatment of Rabbits with Lewisite*, by A. F. Graham, December 1943.

e. (V.21311). *The Effect of BAL on the Arsenic Content of Skin Contaminated with Arsenical Vesicants*, by A. F. Graham and A. C. Chance, February 16, 1944.

f. (Z.3934A). *The Fate of Arsenic in the Body, Following Treatment of Rabbits with Certain Organic Arsenicals*, by A. C. Chance and T. B. B. Crawford, June 10, 1944.

g. (Z.3934B). *The Arsenic Contents of Rabbit Tissues, Urine and Faeces Following the Application of Lewisite I to the Skin: A Note*, by A. C. Chance, June 10, 1944.

h. (Z.9020). *The Effect of BAL in Hastening the Excretion of Arsenicals*, by A. C. Chance, June 1944.

307. University of Manchester (A. R. Todd)

a. (U.15047). *Interim Progress Report on the Double Diazotization Process for DA and DC*, October 17, 1940.

b. (U.18099). *Six-monthly Report (May 1, 1940 to November 1, 1940): I. Heterocyclic Compounds Containing As or Sb as Ring Members. II. The Synthesis of Heterocyclic and Mixed Aromatic Heterocyclic Antimonials. III. Investigation of Synthetic Routes to Derivatives of Diphenyl-stibine Including T.854. IV. Investigation of the Double Diazotization Process for the Manufacture of DA and DC. V. Cyanoformyl Chloride*, by A. R. Todd, December 9, 1940.

c. Report No. 11 (U.21079). *Investigation of the Double Diazotization Process for the Manufacture of DA and DC. Stage IV. Preparation of DA from Diphenylarsenic Acid*, by H. Booker, F. S. Spring, R. H. Stanley, and A. R. Todd, February 14, 1941.

d. Report No. 17 (?). *Investigation of the Double Diazotization Process for the Manufacture of DA and DC. Stage V. The Conversion of Diphenylchloroarsine to Diphenylcyanoarsine*, by P. B. Russell and A. R. Todd, May 1941.

e. Report No. 18. *Investigation of the Double Diazotization Process for the Manufacture of DA and DC. Stage III. The Recovery of Arsenic as Phenyldichloroarsine from Stage II Mother Liquors*, by H. Booker, R. H. Stanley, and A. R. Todd, May 1941.

f. Report No. 19 (V.3957A). *Investigation of the Double Diazotization Process for the Manufacture of DA and DC. Stage I. The Preparation of Phenylarsenic Acid*, by H. Booker, F. S. Spring, R. H. Stanley, and A. R. Todd, May 1941.

g. Report No. 20 (V.3957B). *Six-monthly Report Covering the Period 1st November, 1940 1st May, 1941. Investigation of the Double Diazotization Process for the Manufacture of DA and DC*, by H. Booker, H. T. Openshaw, P. B. Russell, F. S. Spring, R. H. Stanley, A. R. Todd, and W. S. Waring, May 1941.

h. Report No. 21 (V.3957). *Interim Report on the Catalysis of the DA Disproportionation Reaction by Various Metals*, by A. G. Evans, A. R. Todd, and E. Warhurst, May 30, 1941.

i. Report No. 25 (V.15035). *Synthesis of 5:10-Dihydroarsacridine Derivatives*, November 14, 1941.

j. Report No. 26 (V.16084). *3-Methyl-5-chloro-5:10-dihydroarsacridine*, by H. T. Openshaw, F. S. Spring, R. H. Stanley, and A. R. Todd, November 1941.

k. Report No. 27 (V.16206). (*a*) *The Bart Reaction on 4-Aminodiphenylmethane.* (*b*) *5-Cyano-5:10-dihydroarsacridine*, by H. T. Openshaw and A. R. Todd, November 1941.

l. Report No. 29 (V.20072). *4-β-Chloro-ethylthiophenyl Dichloroarsine*, by H. T. Openshaw and A. R. Todd, January 1942.

m. Report No. 30 (V.20746). *The Preparation of 2:5-Dichloro-5:10-dihydroarsacridine and 2-Chloro-5-cyano-5:10-dihydroarsacridine*, by R. E. Davies and A. R. Todd, February 1942.

n. Report No. 33 (W.6146). *Six-monthly Progress Report (Nov. 1, 1941–May 1, 1942): I. Arsacridine Derivatives. II. Other Arsenicals. III. Double Diazotization Process for DA and DC: Purity of Technical Diphenylarsenic Acid (DA Acid). IV. Investigations on Production Methods for N-methyldi-(β-chloroethyl)-amine (S)*, by R. E. Davies, H. T. Openshaw, P. B. Russell, F. S. Spring, A. R. Todd, and J. Wardleworth, June 1942.

o. Report No. 36 (W.13057). *The DA Disproportionation Reaction*, by A. H. Evans, E. Warhurst, and A. R. Todd, September 29, 1942.

p. Report No. 38. *The Arsenic Analogue of S (β:β:-Dichlorodiethylmethylarsine) and Related Compounds*, by R. E. Davies and A. R. Todd, November 1942.

q. Report No. 44 (V.20709). *m-Chloroacetamidophenylchloroarsine (T.307)*, by J. Wardleworth, January 1944.

MISCELLANEOUS

308. (W.12824). *Notes on an Ad Hoc Meeting Held at the Adelphi on September 25, 1942, to Discuss the Formation of Persistent Clouds of War Chemicals, with Special Reference to DC.*

309. *Chemical Warfare Notes for Medical Officers*, August 28, 1942.

310. (Y.8841). *Recent Work in the Pathology and Treatment of War Gas Poisoning*, July 14, 1943.

311. Porton Red Book. Chemical Defence Research Department, *Report on the Chemistry and Toxicology of Certain Compounds*, May 25, 1940.

CANADIAN REPORTS

Experimental Station, Suffield, Alberta

312. Suffield Internal Report No. 8. *Performance of Light Case Bombs Charged Vesicant after Carriage at Low Temperatures*, June 16, 1943.

313. Suffield Report No. 115. *The Casualty Producing Power of Thickened Lewisite Sprayed from Aircraft on Troops*, June 30, 1944.

314. Suffield Technical Minute No. 23. *Vesicant Powers of Lewisite Thickened with Gelva 25*, March 29, 1943.
315. *Chemical Warfare Laboratories Report No. 14*, October 14, 1943.

Extramural Research

316. C.E. 12, November 15-December 15, 1940. *Progress Report*, University of Toronto.
317. C.E. 12, January 1-15, 1941. *Progress Report*, University of Toronto.
318. C.P. 31, *Proceedings of a Conference on Extramural Physiological Investigation Held in Ottawa, March 19, 1943.*
319. C.E. 44 (Rept. No. 6), February 1942. *A Study of the Action of Liquid Mustard Gas on the Rat.*
320. C.E. 44 (Rept. No. 13), C.P. 64, August 1944. *The Antidotal Action of Thiols. IV. The Influence of the Time and Site of Application of BAL on Its Percutaneous Antidotal Activity with Respect to Lewisite*, by S. H. Zbarsky, S. D. Simpson, and L. Young, University of Toronto.
321. C.E. 44 (Rept. No. 14), C.P. 72, November 1944. *The Antidotal Action of Thiols. V. The Influence of the Cutaneous Application of BAL on the Excretion of Arsenic by Rats Dosed with Lewisite*, by S. H. Zbarsky, L. A. Manson, and L. Young, University of Toronto.
322. C.P. 79, C.E. 44 (Rept. No. 18), July 1945. *The Antidotal Action of Thiols. VI. The Synthesis of Radioactive BAL*, by S. D. Simpson and L. Young, University of Toronto.
323. C.P. 80, C.E. 44 (Rept. No. 19), July 1945. *The Antidotal Action of Thiols. VII. The Systemic Distribution of S^{35} Following the Percutaneous Absorption of Radioactive BAL by the Rat*, by S. D. Simpson and L. Young, University of Toronto.

AUSTRALIAN REPORT

324. *Chemical Warfare Physiological Investigations Carried Out at Townsville, Queensland, by Members of the Chemical Warfare Physiology School*, January-February 1943.

INDIAN REPORT

325. CDRE (India) Rept. No. 255. *The Appearances and Treatment of Mustard Gas Burns of the Skin under Indian Conditions*, July 15, 1943.

OPEN LITERATURE

326. Keller, Walter. *The Sensitivity of Human Skin to War Gases of the Yellow Cross Group*, Dermatologica, **85**, 1-26 (1942).
327. Bovida, Giulio. *Experimental Research with Lewisite. Note II. Action of Lewisite on the Skins of the Common Animals Used for Experimentation. Note III. Action of Lewisite on the Human Skin*, La Sperimentale, Archivio di Biologia Normale e Patologica (Organo dell'Accademia Medico-Fisica Fiorentina), **83**, 101-120 (1929).
328. Henderson and Haggard. *Noxious Gases*, 1943.
329. Prentiss, A. M., *Chemicals in War*, McGraw-Hill, 1937.
330. *Medical Manual of Chemical Warfare*, H. M. Stationery Office, 1943.
331. Vedder, E. B., *Medical Aspects of Chemical Warfare*, Williams and Wilkins, 1925.
332. Wachtel, C. *Chemical Warfare*, Chemical Publishing Company, 1941.
333. Mellor, J. W. *A Comprehensive Treatise on Inorganic and Theoretical Chemistry*, Vol. IX, p. 235 (Longmans Green & Co., Ltd., London, 1929).
334. Tatum, A. L. and Cooper, G. A. *An Experimental Study of Mapharsen (meta-Amino para-Hydroxyphenylarsine Oxide as an Antisyphilitic Agent)*, J. Pharm. & Exp. Therapy, **80**, 198 (1934).
335. Lewis, W. L. and Perkins, G. A. *The beta-Chlorovinylchloroarsines*, Industrial and Engineering Chemistry, **15**, 210 (1923).
336. Lewis, W. L. and Stiegler, H. W. *The beta-Chlorovinylarsines and Their Derivatives*, J. Am. Chem. Soc., **47**, 2346 (1925).
337. Green, S. J. and Price, T. S. *The Chlorovinylarsines*, J. Chem. Soc., **119**, 448 (1921).
338. Mann, F. G. and Pope, W. J. *The beta-Chlorovinylarsines*, J. Chem. Soc., **121**, 1754 (1922).
339. Büscher, H. *Grün u Gelbkreuz*, Hamburg, 1932.
340. Mueller, W. *Die Chemische Waffe*, Second Edition, Berlin, 1932.
341. LaCoste, W. and Michaelis, A. *Über Aromatische Arsenverbindungen*, Ann., **301**, 184-261 (1898).
342. Ruff, Otto and Graf, Hugo. *Über das Arsenpentafluorid*, Ber., **39**, 67-71 (1906).

Chapter 8

OSRD FORMAL REPORTS

1. OSRD 527. *The Toxicity of Mustard (Redistilled Lewinstein)*, by Julius M. Cohn, Jules H. Last, Clarence C. Lushbaugh, and George J. Rotarin, University of Chicago Toxicity Laboratory, April 24, 1942. Div. 9-312.1-M1
2. OSRD 1117. *The Preparation and Properties of Alkyl N-Nitroso-N-Alkyl-carbamates and Related Compounds*, by M. S. Kharasch, University of Chicago, December 9, 1942. Div. 9-222.1-M1
3. OSRD 1172. *N-Nitroso-N-chloroethylcarbamic Acid Methyl Ester (TL 188)*, by Max Bergmann and William H. Stein, The Rockefeller Institute for Medical Research, February 2, 1943. Div. 9-222.3-M4
4. OSRD 1272. *N-Nitroso-N-chloroethylcarbamic Acid Methyl Ester (TL 188)*, by Irvin Graef and David Karnofsky, New York University, March 17, 1943.
5. OSRD 1286. *Pulmonary Insufficiency in Rabbits Receiving N-Nitroso-N-chloroethylcarbamic Acid Methyl Ester (TL-188) Intravenously*, by Betty Crawford and Homer W. Smith, New York University, March 23, 1943. Div. 9-322.1-M9
6. OSRD 1313. *A Study of the Hematological Changes Following Exposure to Certain War Gases*, by C. C. Lushbaugh, University of Chicago Toxicity Laboratory, April 3, 1943. Div. 9-385-M1

7. OSRD 1477. *Thermal Data on KB-14 and KB-16*, by Hugh F. Huffman, California Institute of Technology, June 1, 1943. Div. 9-222.3-M5
8. OSRD 2009. *Summary of Work on KB-16*, by Marshall Gates, Technical Aide, Division 9, November 11, 1943. Div. 9-222.3-M6
9. OSRD 3013. *Preliminary Engineering Study of Plant to Manufacture N-Nitroso-(Beta-Chloroethyl)-Methyl Carbamate*, by H. W. Elley, T. W. Stricklin, F. W. Wanderer, J. W. Lund, and J. F. Froning, E. I. duPont de Nemours & Co., August 1, 1944. Div. 9-222.2-M4
10. OSRD 4176. *Status Report on Toxicity and Vesicant Tests of Compounds Referred to the University of Chicago Toxicity Laboratory*, by Hoylande D. Young, University of Chicago Toxicity Laboratory, October 3, 1944. Div. 9-300-M4
11. OSRD 4273. *A Summary of the Vapor Pressures and Volatilities of Compounds Studied at the University of Chicago Toxicity Laboratory*, by C. Ernst Redemann, Saul W. Chaikin, Ralph B. Fearing, Drusilla Van Hoesen, Joseph Savit, Dora Benedict, and George J. Rotariu, University of Chicago Toxicity Laboratory, November 4, 1944. Div. 9-200-M8
12. OSRD 4533. *Organic Arsenicals and Other Toxic Agents*, by C. S. Hamilton, E. J. Crague, Jr., R. J. Andres, R. F. Coles, and Bill Elpern, University of Nebraska, January 1, 1945. Div. 9-219-M4
13. OSRD 5000. *The Effect of Flow Rate on the Toxicities of H, Q, HN1, HN3 and L by Inhalation, by Total Exposure and by Body Exposure*, by Harry G. Albaum, Dora Benedict, Kenneth P. DuBois, Howard G. Glass, James H. M. Henderson, and John O. Hutcheson, University of Chicago Toxicity Laboratory, April 20, 1945. Div. 9-300-M1
14. OSRD 5194. *Tests for Vesicancy on Human Skin*, by John F. Thomson, Hoylande D. Young, Joseph Savit, Eugene Goldwasser, Raymond G. Murray, and Peter DeRuyn, University of Chicago Toxicity Laboratory, June 1, 1945. Div 9-300-M3
15. OSRD 5247. *Paraphenylenediamine Compounds*, by L. I. Smith and V. Engelhardt, University of Minnesota, June 25, 1945. Div. 9-321.3-M1

OSRD INFORMAL REPORTS

16. Contract NDCrc-132, University of Chicago Toxicity Laboratory, E. M. K. Geiling. Inf. Month. Prog. Repts. Div. 9-125-M1
    a. April 16, 1942.
    b. May 16, 1942.
    c. June 15, 1942.
    d. August 19, 1942.
    e. September 22, 1942.
    f. December 31, 1942. Div. 9-125-M2
    g. NDRC 9:1:1 No. 1, February 10, 1943.
    h. NDRC 9:1:1 No. 2, March 10, 1943.
    i. NDRC 9:1:1 No. 3, April 10, 1943.
    j. NDRC 9:1:1 No. 4, May 10, 1943.
    k. NDRC 9:1:1 No. 5, June 10, 1943.
    l. NDRC 9:1:1 No. 6, July 10, 1943.
    m. NDRC 9:1:1 No. 7, August 10, 1943.
    n. NDRC 9:1:1 No. 8, September 10, 1943.
    o. NDRC 9:1:1 No. 9, October 10, 1943.
    p. NDRC 9:1:1 No. 10, November 10, 1943.
    q. NDRC 9:1:1 No. 11, December 10, 1943.
    r. NDRC 9:1:1 No. 12, January 10, 1944.
    s. NDRC 9:1:1 No. 24, January 10, 1945.
17. Contract NDCrc-132, University of Chicago Toxicity Laboratory, E. M. K. Geiling. Special Reports.
    a. No. 1. *Corneal Damage Caused by Tl. 188*, July 24, 1942. Div. 9-322.1-M2
    b. No. 3. *Corneal Damage From Tl. 186 and Tl. 156 (Supplement to Report No. 1)*, August 18, 1942. Div. 9-320-M1
    c. No. 6. *The Determination of the Volatilities and Vapor Pressures of Tl. 188 and Tl. 154*, August 24, 1942. Div. 9-222.3-M2
    d. No. 8. *The Effect of Tl. 188 on Goats, Monkeys, and Dogs*, September 23, 1942. Div. 9-322.1-M3
    e. No. 9. *The Carbamates: I. Toxicity of Tl. 188 in Drinking Water: II. Toxicity Data for Tl. 154 for Mice: III. Eye Effects*, October 31, 1942. Div. 9-322.1-M4
    f. No. 11. *Present Status of Comparative Effects of Amines and Carbamates on the Eye*, November 10, 1942. Div. 9-320-M2
    g. No. 12. *The Pathology of Tl. 188 Poisoning*, November 18, 1942. Div. 9-322.1-M5
    h. No. 13. *The Carbamates: IV. LC_{50} of Tl. 154 For Mice: V. LC_{50} of Tl. 316 For Mice.* (*Supplement to Special Report No. 9*) November 23, 1942. Div. 9-322.2-M1
    i. No. 15. *Present Status of Comparative Effects of Amines and Carbamates on the Eye*, November 23, 1942. Div. 9-320-M2
    j. No. 16. *The Toxicity, Eye Effects, and Pathological Effects of N-(2-chloroethyl)-N-nitroacetamide*, December 11, 1942. Div. 9-325-M1
    k. No. 17. *Tl. 188 (N-(2-chloroethyl)-N-nitromethyl carbamate): A Comparison of the Toxicity of the Plant-run Product with That of the Laboratory Preparation*, December 14, 1942. Div. 9-322.1-M6
18. Contract OEMsr-123, Washington University, C. F. Cori. Inf. Month. Prog. Rept. (NDRC B4-C'), June 19, 1942. Div. 9-312.11-M1
19. Contract OEMsr-282, Northwestern University, W. C. Pierce. Special Report, August 6, 1942. Div. 9-10-M2
20. Contract OEMsr-304, University of Wisconsin, Homer Adkins. Special Report, October 15, 1942. Div. 9-231.2-M1
21. Contract OEMsr-394, University of Chicago, Morris S. Kharasch.
    a. NDRC B3-A Inf. Rept. No. 8. *The Preparation and Properties of KB-10 (Tl. 154) and KB-16 (Tl. 188)*, May 8, 1942. Div. 9-222.3-M1
    b. NDRC 9:2:1 Inf. Rept. No. 6. *Preparation of t-Fluoroethyl Nitrocarbamate*, November 24, 1943. Div. 9-222.3-M1
    c. Inf. Month. Prog. Rept., March 13, 1943.
    d. Inf. Month. Prog. Rept., May 10, 1943.
    e. Inf. Month. Prog. Rept., July 10, 1943.
22. Contract OEMsr-550, New York University, Homer W. Smith. Inf. Month. Prog. Repts. Div. 9-300-M1

a. Rept. (NDRC 14-c) of December 21, 1942.
b. NDRC 9:5:1 No. 1, February 10, 1943.
c. NDRC 9:5:1 No. 2, March 10, 1943.
d. NDRC 9:5:1 No. 11, December 10, 1943.

23. Contract OEMsr-761, E. I. duPont de Nemours & Co., H. W. Elley, Inf. Month. Prog. Repts.
a. August 25, 1942.
b. No. 2, September 15, 1942.
c. No. 3, October 1, 1942.
d. October 15, 1942.
e. Special Report on *The Analysis of KB-16*, October 21, 1942.

24. Contract OEMcmr-24, The Wilmer Institute, Johns Hopkins University, A. C. Woods and J. S. Friedenwald.
a. Rept. No. 30. *The Effects of KB-16 on the Rabbit's Eye*, February 3, 1943. Div. 9-322.1-M7
b. Rept. No. 46. *Inhibition of Mitosis in the Corneal Epithelium: Comparison of the Effects of Mustard, Nitrogen Mustards, L, KB-16 and Certain Derivatives of 1130*, December 15, 1943. Div. 9-384-M3

25. Contract OEMcmr-57, University of Chicago, E. S. Guzman Barron. *Effect of KB-16 on Tissues and Cell Metabolism, and on the Activity of Some Enzyme Systems*, July 1942. Div. 9-322.1-M1

MISCELLANEOUS

26. *NDRC Memorandum on Detection, Protection, Destruction and Eye Symptoms of KB-16*, September 14, 1942.

27. OEMsr-761, E. I. duPont de Nemours & Co., H. W. Elley, Correspondence, August 30, 1943.

UNITED STATES ARMY REPORTS

28. DPGSR 52. *The Assessment of HN1 When Dispersed in Open Terrain Under Semi-tropical Conditions*, December 3, 1945.

29. MRL(EA) Rept. No. 23 *Correlation of Eye Changes in Rabbits with Ct Exposure to H*, June 12, 1944.

30. TDMR 431. *New Compounds HN-2, KB-16 and HN3: Field Tests in 105-mm Shell in Comparison with HS and M1*, September 3, 1942.

31. TDMR 434. *KB-5 Dispersion of KB-16 by Detonation in a Closed Container and in a Field Test in Frangible Grenades*, September 3, 1942.

32. TDMR 464. *Bis(2-chloroethyl)Methylamine; Compound 1137; Mustard: Comparative Eye Action on Guinea Pigs*, November 4, 1942.

33. TDMR 521. *Triethylamine, 2,2'-dichloro. LC_{50} for Mice, 10-min Exposure: Median Detectable Concentration, Vesicant Action: Penetration of Impregnated Cloth: Eye Effects*, December 26, 1942.

34. TDMR 615. *Median Detectable Concentrations by Odor of Plant Run Mustard, Plant Run Lewisite, and Pilot Plant Ethyl Nitrogen Mustard*, April 16, 1943.

35. TRLR 28. *Median Detectable Concentrations by Odor of Vacuum-distilled H, Thiodiglycol H, and Steam-distilled H*, April 12, 1944.

36. TRLR 35. *Mustard: LC_{50} to Goats — 10 Minute Exposure*, June 6, 1944.

37. Med. Div. Inf. Month. Prog. Rept., November 15, 1944.

38. Toxicological Research Laboratory (Edgewood Arsenal). Inf. Month. Prog. Rept. for May 1944, dated June 15, 1944.

UNITED STATES—UNITED KINGDOM REPORTS

Project Coordination Staff (Edgewood Arsenal)

39. PCS Report. No. 9. *Résumé of Recent Knowledge on the Technical Aspects of Chemical Warfare in the Field*, May 17, 1945.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

40. Porton Memorandum No. 15. *Classified List of Compounds Examined Physiologically Since 1919*, October 1941 and *Addendum I*, June 4, 1945.

41. Porton Memorandum No. 24. *The Properties and C.W. Potentialities of T.1702 (KB-16, TL.188)*. April 21, 1943.

42. Porton Memorandum No. 28. *Methods of Decontamination*, April 15, 1944.

43. Porton Report No. 2414. *T.1702. Preparation and Estimation*, August 31, 1942.

44. Porton Report No. 2493. *The Physiological Effects of Various Substances on the Rabbit's Eye: A Preliminary Survey of Chemical Eye Injurants with Particular Reference to Molecular Structure and C.W. Potentialities*, March 7, 1943.

45. Ptn.4000 (T.5415). *Tabular Summary of Properties, Protection, Etc., and Consideration as Alternate Chargings in A C Weapons (Bombs and Spray) of Chemical Warfare Agents*, forwarded by the Chemical Board on April 20, 1943.

46. Ptn.4387 (S.10755). *Comparative Vesicant Power of T.773, S, and T.1702*, August 1942.

47. Ptn.4387 (S.11240) *Preliminary Decontamination Trials with T. 1702*, August 28, 1942.

48. Chemical Defence Research Dept. *Rept. on the Chemistry and Toxicology of Certain Compounds (Porton Red Book)*, May 25, 1940.

Research Establishment, Sutton Oak

49. S.O. R 636. *The Preparation of N-(β-chloroethyl)-N-nitrosomethylurethane (T.1702)*, January 20, 1945.

Extramural Research

50. Cambridge Extramural Testing Station (E. D. Adrian) XZ.124 (Y.2005). *Survey of Toxicities of Fluoroacetates and Related Compounds*, by B. A. Kilby and M. Kilby, March 25, 1943.

51. Cambridge University (H. McCombie). Y.8650. *Report No. 5 on Fluoroacetates and Allied Compounds*, by H. McCombie and B. C. Saunders, May 30, 1943

52. Oxford Eye Hospital — Nuffield Laboratory of Ophthalmology (I. Mann).

a. W.6961. *Accidental Injuries Produced by T.1702*, by Ida Mann and R. H. S. Thompson, July 17, 1942.
b. W.15510. *The Action of T.1702 on the Rabbit's Eye*, by Ida Mann and A. Pirie, 1942 (undated).

53. Oxford University (N. K. Adam). W.11430. *Vapour Pressure of T.1702*, by E. W. Baker, September 28, 1942.
54. Oxford University (R. Robinson)
a. W.4632 C. *Preparation of N-Carbomethoxy-β-chloroethyl Nitramine*, by L. J. Goldsworthy and R. Robinson, May 25, 1942.
b. Robinson Research Report No. 79. *Note on the Preparation of β-chloroethyl Methyl Nitramine*, $Cl{\cdot}CH_2{\cdot}CH_2{\cdot}N(NO){\cdot}CH_3$, by L. J. Goldsworthy and R. Robinson, July 14, 1942.
c. Robinson Research Report No. 80. *Note on the Preparation of N-Carbomethoxy β-Bromoethyl Nitramine*, $Br{\cdot}CH_2{\cdot}CH_2{\cdot}N(NO){\cdot}CO_2CH_3$, by L. J. Goldsworthy and R. Robinson, July 22, 1942.

MISCELLANEOUS

55. V.18209. *Commentary on the Aggressive Power of Trichlortriethylamine*, by D. G. Cordier, March 12, 1941.

OPEN LITERATURE

56. Bruhl, J. W. *Berichtung zu Meiner Mittheilung über das optische Verhalten und die Constitution der Nitramidkylurethane und des Anthranils*. Ber., **36**, 4294–4295 (1903).
57. Carothers, W. H. (Editor). *Organic Syntheses*, **13**, 84 (1933).
58. Klobbie, M. E. A. *Action de l'acide azoteux sur les corps azotés*. Rec. Trav. Chim., **9**, 134–154 (1890).
59. v. Pechmann, H. *Über Diazomethan und Nitrosoacylamine*. Ber., **31**, 2640 2646 (1898).
60. Schmidt, O. *Beiträge zur Spektrochemie des Stickstoffs*. Z. für Physikal. Chem., **58**, 513–540 (1907).
61. Ward, K., Jr. *The Chlorinated Ethylamines — A New Type of Vesicant*. J. Am. Chem. Soc., **67**, 914 916 (1935).

Chapter 9

OSRD FORMAL REPORTS

1. OSRD 1284. *Possible Toxic Agents and Intermediates*, by M. S. Kharasch, University of Chicago, March 22, 1943. Div. 9-200-M5
2. OSRD 1294. *The Preparation of Ethyldichloramine and Related Compounds*, by M. S. Kharasch, University of Chicago, March 23, 1943. Div. 9-213.14-M5
3. OSRD 1295. *The Decontamination of Dialkyl Fluorophosphates*, by Homer Adkins and A. L. Wilds, University of Wisconsin, March 24, 1943. Div. 9-521-M1
4. OSRD 3078. *Preparation of Alkyl Fluorophosphates*, by R. L. Jenkins and E. E. Hardy, Monsanto Chemical Company, January 5, 1944. Div. 9-211.12-M3
5. OSRD 3113. *Description of Process, Preliminary, Diisopropyl Fluorophosphate, Batch Method*, by R. L. Jenkins, W. M. Cooper, E. E. Hardy, and R. F. Walters, Monsanto Chemical Company, January 11, 1944. Div. 9-211.11-M1
6. OSRD 3228. *Description of Process, Preliminary, Diisopropyl Fluorophosphate, Continuous Method*, by R. L. Jenkins, W. M. Cooper, and R. F. Walters, Monsanto Chemical Company, February 1, 1944. Div. 9-211.11-M2
7. OSRD 3480. *Colorimetric Determination of Fluorine in Fluoro-organic Compounds*, by J. H. Yoe, L. G. Overholser, University of Virginia, April 14, 1944. Div. 9-422.3-M1
8. OSRD 3481. *Determination of Fluorine in Fluoro-organic Compounds*, by J. H. Yoe, J. M. Salsbury, and J. W. Cole, University of Virginia, April 14, 1944. Div. 9-422.3-M2
9. OSRD 3830. *Determination of Fluorine in Fluoro-organic Compounds in Low Concentrations in Air*, by J. H. Yoe, J. M. Salsbury, and J. W. Cole, University of Virginia, June 27, 1944. Div. 9-422.3-M3
10. OSRD 4012. *The Preparation of New Toxic Gases*, by Anton B. Burg, The University of California at Los Angeles, August 12, 1944. (Division 10) Div. 10-402.36-M8
11. OSRD 4176. *Status Report on Toxicity and Vesicant Tests of Compounds Referred to the University of Chicago Toxicity Laboratory*, by E. M. K. Geiling, R. K. Cannan, W. Bloom, and H. D. Young, University of Chicago Toxicity Laboratory, October 3, 1944. Div. 9-300-M4
12. OSRD 4273. *A Summary of the Vapor Pressures and Volatilities of Compounds Studied at the University of Chicago Toxicity Laboratory*, by C. E. Redemann, S. W. Chaikin, R. R. Fearing, D. Van Hoesen, J. Savit, D. Benedict, and G. J. Rotariu, University of Chicago Toxicity Laboratory, November 4, 1944. Div. 9-200-M8
13. OSRD 4620. *A Systematic Scheme for the Detection of Toxics on Plain Silica Tubes*, by D. S. Tarbell, R. B. Carlin, V. P. Wystrach, E. Klingsberg, J. F. Bunnett, and E. G. Lindstrom, University of Rochester, January 24, 1945. Div. 9-421.2-M2
14. OSRD 4843. *The Detection of Organic Fluorine Toxics. The Use of Thiocarbazones as Arsenical Detectors*, by N. L. Drake, University of Maryland, April 19, 1945. Div. 9-422.8-M14
15. OSRD 5000. *The Effect of Flow Rate on the Toxicities of H, Q, HN1, HN3 and L by Inhalation, by Total Exposure and by Body Exposure*, by Harry G. Allaun, Dora Benedict, Kenneth P. DuBois, Howard G. Glaw, James H. M. Henderson, and John O. Hutcheon, University of Chicago Toxicity Laboratory, April 28, 1945. Div. 9-300-M1
16. OSRD 5146. *Final Report Under Contract OEMsr-532*, by Barnett Cohen, Joseph Harris, E. R. Van Artsdalen, and Marie E. Perkins, The Johns Hopkins University, May 29, 1945. Div. 9-200-M10
17. OSRD 5148. *Studies in the Synthesis of Organic Compounds of Sulfur, Nitrogen and Chlorine Which Possess Physiological Activity*, by R. C. Fuson, C. C. Price, and H. R. Snyder, University of Illinois, May 29, 1945. Div. 9-212.5-M4

18. OSRD 5194. *Tests for Vesicancy on Human Skin*, by J. F. Thomson, H. D. Young, J. Savit, E. Goldwasser, E. M. K. Geiling, R. K. Cannan, and William Bloom, University of Chicago Toxicity Laboratory, June 1, 1945. Div. 9-300-M3

19. OSRD 5305. *Supplement to OSRD 4176. Status Report on Toxicity and Vesicant Tests of Compounds Referred to the University of Chicago Laboratory*, by E. M. K. Geiling, R. K. Cannan, and William Bloom, July 4, 1945. Div. 9-300-M5

20. OSRD 5345. *The Chemistry of PF-3 as a Water Contaminant*, by C. C. Price and B. H. Velzen, University of Illinois, August 10, 1945. Div. 9-211.11-M3

21. OSRD 5391. *Vesicant Studies*, by Duncan A. MacInnes and D. Belcher, The Rockefeller Institute for Medical Research, August 10, 1945. (Division 11) Div. 11-203.512-M13

22. OSRD 5483. *The Preparation of Ethanefluorophosphonic Acid, Isopropyl Ester (KB-280) — The Ethyl Analog of T-144*, by M. S. Kharasch, E. V. Jensen, and R. L. Adelman, University of Chicago, August 20, 1945. Div. 9-211.4-M2

23. OSRD 6118. *The Determination of MCE*, by T. S. Lee, J. W. Sease, and Carl Niemann, California Institute of Technology, October 16, 1945. Div. 9-422.43-M1

24. OSRD 6391. *The Preparation of MCE and MFI*, by R. L. Jenkins and E. E. Hardy, Monsanto Chemical Company, December 31, 1945. Div. 9-211.5-M2

25. OSRD 6400. *An Investigation of a New Group of German War Gases*, by R. C. Fuson, L. J. Reed, B. H. Velzen, J. C. Bailar, Jr., and C. C. Price, University of Illinois, December 1, 1945. Div. 9-211.5-M1

OSRD INFORMAL REPORTS

26. Contract NDCrc-132, University of Chicago Toxicity Laboratory, E. M. K. Geiling. Inf. Month. Prog. Repts. on Toxicity of Chemical Warfare Agents (NDRC B4-A and 9:4:1). Div. 9-125-M1 Div. 9-125-M2

a. Rept. of September 22, 1942.
b. Rept. of October 24, 1942.
c. Rept. of November 17, 1942.
d. Rept. of December 31, 1942.
e. 9:4:1 No. 1, February 10, 1943.
f. 9:4:1 No. 2, March 10, 1943.
g. 9:4:1 No. 3, April 10, 1943.
h. 9:4:1 No. 4, May 10, 1943.
i. 9:4:1 No. 5, June 10, 1943.
j. 9:4:1 No. 6, July 10, 1943.
k. 9:4:1 No. 8, September 10, 1943.
l. 9:4:1 No. 10, November 10, 1943.
m. 9:4:1 No. 11, December 10, 1943.
n. 9:4:1 No. 12, January 10, 1944.
o. 9:4:1 No. 13, February 10, 1944.
p. 9:4:1 No. 14, March 10, 1944
q. 9:4:1 No. 15, April 10, 1944.
r. 9:4:1 No. 16, May 10, 1944.
s. 9:4:1 No. 22, November 10, 1944.
t. 9:4:1 No. 24, January 10, 1945.
u. 9:4:1 No. 25, February 28, 1945.

27. Contract OEMsr-97, Iowa State College, Henry Gilman. Inf. Month. Prog. Repts. Div. 9-122-M1 Div. 9-122-M2
a. May 1942.
b. June 1942.
c. September 1942.
d. October 1942.
e. November 1942.
f. December 1942.
g. January 1943.
h. February 10, 1943.
i. March 10, 1943.
j. April 10, 1943.
k. May 10, 1943.
l. June 10, 1943.
m. July 10, 1943.
n. August 10, 1943
o. September 10, 1943.
p. November 10, 1943.
q. December 10, 1943.
r. February 10, 1944.

28. Contract OEMsr-209, University of Illinois, L. F. Audrieth and J. C. Bailar. Inf. Repts.
a. NDRC B-6 Inf. Rept. No. CXLI on *Vapor Pressure of Arsine Dissolved in Thionyl Chloride p-Ethyl-nitrobenzene, 1-Nitropropane, Triethyl Borate, and Tributyl Borate*, June 17, 1942. Div. 9-213.1-M1
b. NDRC B-6 Inf. Rept. No. CXL on *The Dialkyl Monofluophosphates*, June 16, 1942. Div. 9-211.12-M1
c. NDRC B-6 Inf. Rept. No. CLVII on *Fluophosphates and Related Compounds*, July 15, 1942. Div. 9-211.1-M1
d. NDRC B-6 Inf. Rept. No. CLXXX on *Vapor Pressures of Diethyl Fluophosphate, Ethyl Difluophosphate, Dimethyl Fluophosphate, Ethyl Fluoantfonate, and Trimeric Phosphonitrilic Chloride*, August 15, 1942. Div. 9-252-M2
e. NDRC B-6 Inf. Rept. No. CLXXXVIII on *The Alkyl Difluophosphates and the Mono- and Difluothiophosphates*, September 15, 1942. Div. 9-211.12-M2
f. Inf. Rept. on *Fluophosphates and Related Compounds*, October 15, 1942. Div. 9-211.1-M1
g. Inf. Rept. on *Fluophosphates and Related Compounds*, November 15, 1942. Div. 9-211.1-M1
h. Inf. Rept. on *Fluophosphates and Related Compounds* — VI, December 15, 1942. Div. 9-211.1-M1
i. Inf. Rept. on *Fluophosphates and Related Compounds* — VIII, February 15, 1943. Div. 9-211.1-M1
j. Inf. Rept. on *Fluophosphates and Related Compounds* — X, April 15, 1943. Div. 9-211.1-M1
k. Inf. Rept. on *A New Method for the Synthesis of Phosphoryl Chlorofluoride POClF*, August 15, 1943. Div. 9-211.2-M1
l. Inf. Rept. on *Fluophosphates and Related Compounds* — XII, October 15, 1943.

m. Inf. Rept. on *Fluophosphates and Related Compounds*, November 15, 1943. Div. 9-211.1-M1

29. Contract OEMsr-304, University of Wisconsin, Homer Adkins. Inf. Month. Prog. Rept., May 9, 1942. Div. 9-364-M2

30. Contract OEMsr-304, University of Chicago, M. S. Kharasch. Inf. Month. Prog. Repts. Div. 9-211.4-M2
   a. April 15, 1943.
   b. May 10, 1943.
   c. June 10, 1943.
   d. August 10, 1943.
   e. September 8, 1943.
   f. October 9, 1943.
   g. June 13, 1945.

31. Contract OEMsr-363, University of Illinois, Charles C. Price. Inf. Month. Prog. Repts. Div. 9-223.1-M5
   a. January 10, 1944.
   b. May 10, 1944.
   c. June 10, 1944.

32. Contract OEMcmr-24, Wilmer Institute, The Johns Hopkins University, A. C. Woods and J. S. Friedenwald.
   a. Rept. No. 40. *Studies on the Ocular Reactions of Rabbits to Di-isopropyl Fluorophosphate (PF3)*, by R. C. Scholz, September 20, 1943. Div. 9-311.1-M1
   b. Rept. No. 42. *The Protection of PF3 Poisoned Rats and Mice by the Systemic Administration of Drugs*, by J. S. Friedenwald and R. O. Scholz, October 19, 1943. Div. 9-521-M2
   c. Rept. No. 43. *The Effect of PF3 on Human Eyes*, by R. O. Scholz and L. J. Wallen, November 22, 1943. Div. 9-311.1-M2

33. Contract OEMcmr-245, Cornell University Medical College, McKeen Cattell.
   a. Rept. No. 21. *Pharmacology of PF3 in the Cat*, by McKeen Cattell and Harry Gold, June 16, 1945. Div. 9-311.1-M4
   b. Rept. No. 22A. *PF3 in Myasthenia Gravis*. Div. 9-526-M2

34. Contract OEMsr-97, Iowa State College, Henry Gilman. Correspondence.
   a. July 2, 1942.
   b. August 4, 1942.

35. Contract OEMsr-304, University of Chicago, M. S. Kharasch. Correspondence.
   a. October 21, 1943.
   b. June 21, 1945.

MISCELLANEOUS

36. Contract OEMsr-845, Monsanto Chemical Company. R. L. Jenkins and E. E. Hardy. *Miscellaneous Report on the Physiological Action of PF-3 as Observed During Laboratory and Pilot Plant Investigation of this Compound*, undated. Div. 9-311.1-M5

37. NDRC Division 9 Informal Memorandum No. 4. *Summary of Data on Di-isopropyl Fluorophosphate and Related Compounds*, by Homer W. Smith and Marshall Gates, October 1, 1944. Div. 9-311.1-M3

UNITED STATES ARMY REPORTS

Chemical Warfare Service

38. EATR 78. *Constants and Physiological Action of Chemical Warfare Agents*, July 19, 1932.

39. EATR 251. *The Detection of Hydrocyanic Acid by Odor*, March 31, 1938.

40. Medical Division Rept. No. 1. *Miosis of the Pupil as a Test for Water Contamination by PF-3*, September 28, 1944.

41. Medical Division Rept. No. 6. *The Detection of Organic Fluorine Compounds in Water*, October 31, 1944.

42. Medical Division Rept. No. 7. *Field Testing of Spot Test Procedure for Detection of Fluoro-Organic Compounds in Water*, March 8, 1945.

43. Medical Division Rept. No. 29. *The Mechanism of Detoxification of PF3 and Related Fluorophosphates in the Animal Organism*, March 30, 1945.

44. Medical Division Rept. No. 35. *The Regeneration of Cholinesterase Activity in PF3 Poisoning and the Effect of Injected Cholinesterase Preparations in Normal and PF3 Poisoned Animals*, June 21, 1945.

45. Medical Division Rept. No. 48. *Mode of Action of Substituted Carbamic Esters and a Comparison of Their Action on Acetylcholine Esterase Activity with that of Di-isopropyl Fluorophosphate in Vivo and in Vitro*, August 28, 1945.

46. Medical Division Rept. No. 69. *The Relationship Between Cholinesterase Inhibition and the Pharmacological Action of PF3*, January 30, 1946.

47. Medical Division Rept. No. 71. *The Chronic Toxicity of PF3 in Dogs, Monkeys and Rats*, January 31, 1946.

48. MRL(EA) Rept. No. 25. *The Mechanism of In Vitro and In Vivo Inhibition of Cholinesterase Activity by PF-3 in the Rabbit, Monkey, and Man*, May 10, 1944.

49. TDMR 540. *Dimethyl, Diethyl, and Diisopropyl Fluorophosphates: LC_{50}: Toxicity by Skin Absorption; Median Detectable Concentration; Eye Effects and Speed of Action*, January 28, 1943.

50. TDMR 613. *Quantitative Determination of Fluorophosphates*, April 7, 1943.

51. TDMR 615. *Median Detectable Concentrations by Odor of Plant Run Mustard, Plant Run Lewisite, and Pilot Plant Ethyl Nitrogen Mustard*, April 16, 1943.

52. TDMR 628. *Diisopropyl Fluorophosphate: Effectiveness as an Incapacitating Agent*, May 1, 1943.

53. TDMR 651. *The Pharmacodynamics of Diisopropyl Fluorophosphate*, May 18, 1943.

54. TDMR 674. *The Effect of Several Chemical Warfare Agents on the Kratschmer's Reflex in Rabbits*, June 10, 1943.

55. TDMR 698. *Fluorophosphates and Cyanides: A Method of Evaluating their Speed of Action, Rate of Detoxication, and Toxicity*, August 30, 1943.

56. TDMR 832. *Diisopropyl Fluorophosphate*, May 1, 1944.

57. TDMR 854. *Protection Afforded by Canisters Against Diisopropyl Fluorophosphate and Dimethyl Fluorophosphate*, June 28, 1944.

58. TDMR 887. *Identification of Agents Containing Fluorine: I. Use of Plain Silica Gel Tubes*, September 8, 1944.

59. TDMR 1064. *Protection Afforded by Canisters Against Methyl Ethyl Fluorophosphate*, May 24, 1945.

60. TDMR 1094. *Physical Constants of MCE*, July 16, 1945.
61. TDMR 1121. *The Hydrolysis of MCE*, August 27, 1945.
62. TDMR 1123. *Compound MCE: Estimation of Concentration in Air and Sorption by Charcoal*, August 21, 1945.
63. TRLR 9. *Diisopropyl Fluorophosphate: Physiological Effectiveness on Primates*, October 25, 1943.
64. TRLR 21. *Diisopropyl Fluorophosphate: Physiological Effectiveness on Primates, Study No. 2*, December 31, 1943.
65. TRLR 28. *Median Detectable Concentrations by Odor of Vacuum-distilled H, Thiodiglycol H, and Steam-distilled H*, April 12, 1944.
66. Medical Division (Edgewood Arsenal) Inf. Month. Prog. Repts.
    a. October 1944.
    b. December 1944.
    c. January 1945.
    d. February 1945.
    e. March 1945.
    f. April 1945.
    g. May 1945.
    h. June 1945.
    i. July 1945.
    j. August 1945.
    k. September 1945.
    l. October 1945.
    m. November 1945.
    o. January 1946 (Quarterly Progress Report).
    p. April 1946 (Quarterly Progress Report).
67. Medical Research Laboratory (Edgewood Arsenal), Inf. Month. Prog. Repts.
    a. August 1943.
    b. September 1943.
    c. October 1943.
    d. November 1943.
    e. December 1943.
    f. March 1944.
    g. May 1944.
68. Toxicological Research Laboratory (Edgewood Arsenal), Inf. Month. Prog. Repts.
    a. July 1944.
    b. August 1944.
69. Contract W-40-057-CWS-23, University of Chicago Toxicity Laboratory. Inf. Month. Prog. Repts. on *Toxicity and Irritancy of Chemical Agents.*
    a. No. N.S. 1, April 15, 1945.
    b. No. N.S. 2, May 15, 1945.
    c. No. N.S. 3, June 15, 1945.
    d. No. N.S. 4, July 15, 1945.
    e. No. N.S. 5, August 15, 1945.
    f. No. N.S. 7, October 15, 1945.
    g. No. N.S. 8, December 15, 1945.
    h. No. N.S. 9, February 15, 1946.
    i. No. N.S. 11, June 15, 1946.
70. Memorandum for the Chief, Chemical Warfare Service, on *New German Toxic Agent (A 10)*, May 21, 1945.

MISCELLANEOUS

71. First General Hospital, 814th Hospital Center, APO 887. *Memorandum on Clinical Report of Accidental Chemical Warfare Injury Due to Agent L 100*, May 14, 1945.
72. Intelligence Division Report No. 3895. *Technical Information on Tabun and Sarin*, June 8, 1945.
73. Intelligence Division Report No. 4006. *German Views on Pharmacology and Therapeutics of War Gases*, August 22, 1945.
74. Intelligence Division Report No. 3874. (CIOS Evaluation Report No. 11, CIC 75 4). *Information on a New Group of Toxic War Gases*, April 24, 1945.

UNITED STATES NAVY REPORTS

Naval Research Laboratory

75. S-877-2 (459-HWC/EAR). *The Adsorption of Diisopropyl Fluorophosphate by Impregnated Charcoal*, May 10, 1943.

OFFICE OF STRATEGIC SERVICES REPORTS

76. Letter with Enclosures, A. G. Noble (Major, CWS) to W. R. Kirner, Chief NDRC Division 9, September 20, 1944.

BRITISH REPORTS

Chemical Defence Research Station, Porton

77. Porton Memorandum No. 15. *Classified List of Compounds Examined Physiologically Since 1919*, October 1941, and Addendum 1, June 4, 1945.
78. Porton Report No. 2370 (Addendum). *A Suggested Method of Using the Range-Finder in Gas Chamber and Field Work*, June 3, 1942.
79. Porton Report No. 2441. *Assessment of the Harassing Effects of Diisopropyl Fluorophosphate and Diethyl Fluorophosphate*, October 31, 1942.
80. Porton Report No. 2540. *A New Titrimetric Method for the Estimation of Fluorine*, October 8, 1943.
81. Porton Report No. 2557. *The Estimation of Organic Fluorine Compounds. Part II. Dialkyl Fluorophosphates.* February 4, 1944.
82. Porton Report No. 2580. *Tris(β-Chloroethylthio)Phosphine (T.1063) and Related Compounds*, January 26, 1944.
83. Porton Report No. 2589. *Toxicity of T.1703 Vapour*, January 28, 1944.
84. Porton Report No. 2592. *An Investigation into the Potentiation of Diisopropyl Fluorophosphate Vapour in Respect of the Production of Eye Casualties*, February 3, 1944.
85. Porton Report No. 2593. *Kinetics of Hydrolysis of Diisopropyl Fluorophosphate (T.1703)*, February 2, 1944.
86. Porton Report No. 2632. *The Toxicity and Stability of PF-3 and T.2002*, July 17, 1944.
87. Porton Report No. 2693. *The Toxicity, Symptoms, Pathology, and Treatment of T.2104 Poisoning in Animals*, August 16, 1945, and *Addendum I*, September 27, 1945.
88. Porton Report No. 2698. *Eye Effects of T.2104*, September 28, 1945.
89. Ptn. 4000 (T.5415). *Tabular Summary of Properties, Protection, etc., and Consideration on Alternate Chemicals*

in A C Weapons (Bombs and Spray) of Chemical Warfare Agents, April 20, 1943.

90. Ptn. 4240 (V.3956). *Laboratory Examination of Filling in German Green Ring 3 Gas Shell*, May 4, 1945.
91. Ptn. 4240 (V.6912). *Rate of Evaporation and Detectability by Smell of the Compound T.2104*, August 7, 1945.
92. Ptn. 4080 (S.7814). *Physiological Tests on Phosphorus Oxychloride and Phosphorus Pentachloride*, by A. Fairley, June 5, 1942.
93. Ptn. 4280 (T.1980). *Fluorophosphates and Fluoroacetates*, July 27, 1943.
94. Ptn. 4280 (T.14339). *Progress of Work on Fluoroacetates and Fluorophosphates: 1st Interim Report*, November 2, 1943.
95. Ptn. 4280 (T.16181). *The Detection of C.W. Agents Containing Fluorine: 2nd Interim Report*, December 4, 1943.
96. Ptn. 4280 (T.5007). *The Detection of C.W. Agents Containing Fluorine: 3rd Interim Report*, April 24, 1944.
97. Ptn. 4280 (T.9410). *The Detection of C.W. Agents Containing Fluorine: 4th Interim Report*, July 20, 1944.
98. Ptn. 4281 (T.8789). *Determination of Basic Data on the Rate of Evaporation of PF-3 in the Field*, July 17, 1944.
99. Z.8179. *Storage of AF-1 and PF-3*, July 22, 1944.

Research Establishment, Sutton Oak

100. S.O. 685. *Di-isopropyl Fluorophosphate Incident, Sutton Oak*, September 14, 1934.
101. S.O. R 686. *An Improved Method for the Determination of Fluorine in Aliphatic Fluoro-Compounds and Fluorophosphates*, April 28, 1944.
102. Y.18389. *Notes on Preparation of Methyl Fluoroacetate, Fluoroethyl Alcohol, and Diisopropyl Fluorophosphate*, December 20, 1943.

Extramural Research

103. Cambridge Biochemical Laboratory (M. Dixon) W.1259. *Mode of Action of Fluorophosphate Esters, with an Enzyme Test for their Potency*, by J. F. Muckworth, March 1942.
104. Cambridge Extramural Testing Station (E. D. Adrian)
    a. NZ.71 (V.13335). *Physiological Examination of Dimethyl Fluorophosphate*, by H. McCombie, E. D. Adrian, B. A. Kilby, and M. Kilby, October 8, 1941.
    b. NZ.92 (V.23246A). *Physiological Examination of a Number of Alkyl Fluorophosphates*, by B. A. Kilby, M. Kilby, H. McCombie, and B. C. Saunders, March 4, 1942.
    c. NZ.93 (V.23246B). *Physiological Examination of Ethyl Metaphosphate and Diethyl Chlorophosphate*, by H. McCombie, B. A. Kilby, M. Kilby, and B. C. Saunders, March 4, 1942.
    d. NZ.101 (W.3588). *The Physiological Examination of 3,3-Di-(Thiethyl)Diethylmethylamine and Diethyl Thiocyanophosphate*, by H. McCombie, B. A. Kilby, M. Kilby, and E. D. Adrian, May 11, 1942.
    e. NZ.103 (W.8496). *Physiological Examination of Dimorpryl Fluorophosphate*, by E. D. Adrian, B. A. Kilby, and M. Kilby, August 12, 1942.
    f. NZ.105 (W.10490). *Physiological Examination of Certain Phosphate Esters*, by B. A. Kilby and M. Kilby, September 10, 1942.
    g. NZ.109 (W.12283). *Physiological Examination of Certain Phosphate Esters. II*, by B. A. Kilby and M. Kilby, October 8, 1942.
    h. NZ.111 (W.14380). *Physiological Examination of Diisopropyl Fluorophosphate*, by A. M. Barrett, W. Feldberg, B. A. Kilby, and M. Kilby, November 10, 1942.
    i. NZ.114 (W.15280). *Physiological Examination of Di-sec-butyl Fluorophosphate*, by B. A. Kilby and M. Kilby, November 20, 1942.
    j. NZ.116 (W.17732). *Physiological Examination of Certain Phosphate Esters. III*, by B. A. Kilby and M. Kilby, January 7, 1943.
    k. NZ.118 (W.17732). *Physiological Examination of Phosphorus Oxyfluoride (T.1102)*, by B. A. Kilby and M. Kilby, January 7, 1943.
    l. NZ.127 (V.5444). *Physiological Examination of Dicyclohexyl Fluorophosphate (T.1840)*, by B. A. Kilby and M. Kilby, May 25, 1943.
    m. NZ.131 (V.7833). *Second Survey of Toxicities of Fluoroacetates and Related Compounds*, by B. A. Kilby and M. Kilby, June 10, 1943.
    n. NZ.142 (V.10088). *Summary of Work on the Treatment of Fluoroacetate and Fluorophosphate Poisoning. I*, by E. D. Adrian, K. J. Carpenter, and B. A. Kilby, November 15, 1943.
    o. NZ.143 (V.17176). *The Toxicities of Eight Substituted Aminophosphoryl Fluorides*, by K. J. Carpenter and B. A. Kilby, November 25, 1943.
    p. NZ.144 (V.19409A). *Third Survey of Toxicities of Fluoroacetates and Related Compounds*, by K. J. Carpenter and B. A. Kilby, December 20, 1943.
    q. NZ.154. *Examination of Dimethylaminosulphuryl Chloride and Fluoride*, by K. J. Carpenter and B. A. Kilby, March 6, 1944.
    r. NZ.162 (Z.9035). *Toxicity Examination of Various Compounds*, by K. J. Carpenter and B. A. Kilby, August 24, 1944.
    s. NZ.170. *Preliminary Report on Toxicity and Physiological Action of T.2104*, E. D. Adrian, K. J. Carpenter, and B. A. Kilby, May 3, 1945.
    t. NZ.171. *Toxicity Examination of Isopropoxymethylphosphoryl Fluoride (T.2109) and Two Analogues*, by K. J. Carpenter, June 28, 1945.
105. Cambridge University (H. McCombie)
    a. V.17289. *Report No. 1 on Fluorophosphates. The Alkyl Fluorophosphates*, by B. C. Saunders, December 18, 1941.
    b. V.21923. *Report No. 2 on Fluorophosphates. Interim Report on Alternative Methods of Synthesising Alkyl Fluorophosphates*, by H. McCombie and B. C. Saunders, forwarded by the Chemical Board, February 27, 1942.
    c. V.21455. *Interim Report No. 3 on Alkyl Fluorophosphates (Dialkoxy-Phosphoryl-Fluorides)*, by H. McCombie and B. C. Saunders, March 28, 1942.
    d. W.3300. *Report No. 4 on Fluorophosphates*, by H. McCombie and B. C. Saunders, May 20, 1942.

e. W.8285. *Report No. 5 on Fluorophosphates*, by H. McCombie, August 8, 1942.

f. W.12286. *Report No. 6 on Fluorophosphates and Allied Compounds*, by H. McCombie and B. C. Saunders, September 30, 1942.

g. W.10309. *Report No. 7 on Fluorophosphates*, by H. McCombie and B. C. Saunders, January 16, 1943.

h. Y.2121. *Modifications in the Preparation of Di-isopropyl Fluorophosphate (Semi-Technical Scale). Report No. 8 on Fluorophosphates*, by H. McCombie and B. C. Saunders, March 1, 1943.

i. Y.3[illegible]4. *Preparation of Dicyclohexyl Fluorophosphate (T.1830). Report No. 9 on Fluorophosphates*, by H. McCombie and B. C. Saunders, April 10, 1[illegible]

j. Y.5[illegible]9. *Report No. 10 on Fluorophosphates. Di-β-Fluoroethyl Fluorophosphate (Di-β-Fluoroethoxy Phosphoryl Fluoride)*, by H. McCombie and B. C. Saunders, May 22, 1943.

k. Y.6508. *Report No. 11 on Fluorophosphates and Allied Compounds*, by H. McCombie and B. C. Saunders, May 27, 1943.

l. Y.11630. *Fluorophosphates. Report No. 13. Improved Preparation of Sec-Butyl Fluorophosphate. T.1835*, by H. McCombie and B. C. Saunders, August 24, 1943.

m. Y.16561. *Report No. 14 on Fluorophosphates and Allied Compounds*, by H. McCombie and B. C. Saunders, September 30, 1943.

n. Y.18702. *A New Type of Fluorophosphate: Amino Alkoxy Phosphoryl Fluorides. Report No. 15 on Fluorophosphates*, by H. McCombie and B. C. Saunders, December 9, 1943.

o. Y.20063. *Report No. 16 on Fluorophosphates. An Alternative Method of Preparing Aminophosphoryl Fluorides*, by H. McCombie and B. C. Saunders, December 30, 1943.

p. Y.20497. *Report No. 17 on Fluorophosphates*, by H. McCombie and B. C. Saunders, December 31, 1943.

q. Z.6930. *Report No. 18 on Fluorophosphates and Allied Compounds*, by H. McCombie and B. C. Saunders, July 4, 1944.

r. *Report No. 19 on Fluorophosphates and Allied Compounds*, by H. McCombie and B. C. Saunders, June 22, 1945.

s. *Report No. 20 on Fluorophosphates and Related Compounds*, by H. McCombie and B. C. Saunders, June 23, 1945.

t. Y.20784. *Determination of Fluorine in Organic Compounds*, by H. McCombie and B. C. Saunders, December 31, 1943.

106. Imperial College of Science and Technology (H. V. A. Briscoe)

a. V.5591. *The Suitability of Certain Volatile Fluorine Compounds as War Gases*, by H. V. A. Briscoe and H. J. Emeleus, May 30, 1941.

b. V.3072. *Summary of Investigations on Volatile Fluorine Compounds Carried Out at the Imperial College, London, June 1940-June 1941.*

c. W.9915. *Provisional Assessment of the Value of Fluorine Compounds as C.W. Agents*, H. V. A. Briscoe and H. J. Emeleus, September 2, 1942.

d. *Summary of Available Information on PF_3, ClF_3, and BrF_3*, by H. V. A. Briscoe and H. J. Emeleus, October 23, 1942.

e. Y.3440. *The Analysis of Organic Fluoro Compounds Modifications of the de Boer Zirconium-alizarin Reagent*, by H. V. A. Briscoe and H. J. Emeleus, April 15, 1943.

f. Y.7333. *The Analysis of Organic Fluorine Compounds. Part II*, by H. V. A. Briscoe and H. J. Emeleus, June 7, 1943.

107. University College, Southampton (N. K. Adam). Y.15308. *The Vapour Pressure of Diisopropyl and Di-sec-butyl Fluorophosphates*, by E. W. Balson, October 21, 1943.

MISCELLANEOUS

108. C. D. Report No. 1076. *Chemical, Physical and Physiological Properties of Certain Volatile Fluorine Compounds*, March 3, 1941.

109. W.11821. *Notes on a Meeting of the Panel of Ophthalmic Specialists Held on January 21, 1943*, February 10, 1943.

110. Y.6597. *Notes of a Meeting of the Panel of Ophthalmic Specialists Held at the Ministry of Supply on May 20, 1943*, June 10, 1943.

111. Y.18709 and Correction Y.19930. *Summary of British Work on Fluoroacetates and Fluorophosphates from August 25, 1943 to January 10, 1944.*

112. A.2156.CDR5. *Summary of Intelligence on Enemy CW and Smoke*, April 22-May 6, 1945.

113. A.7578. *CDR5. Enemy CW and Smoke Intelligence Summary No. 82*, September 27, 1945.

114. *German Le-100: Porton T.2104*, by R. C. Eley, May [illegible], 1945.

OPEN LITERATURE

115. Arbusow. Zentralblatt II 1640 (1906).

116. Booth and Dutton. J. Am. Chem. Soc., **61**, 2937 (1939).

117. Lange. Ber., **65B**, 1568 (1932).

118. Marquina. Revista de la Academia de Ciencias Exactas, **30**, 382 (1933).

Chapter 10

OSRD FORMAL REPORTS

1. OSRD 1023. *Fluorocarbons*, by W. T. Miller and A. L. Henne, Cornell University and Ohio State University, October 14, 1942. Div. 9-232-M1

2. OSRD 1222. *Fundamental Factors in the Design of Protective Respiratory Equipment*, by Leslie Silverman, Robert C. Lee, George Lee, Katherine R. Drinker, and Thorne M. Carpenter, March 4, 1943.

3. OSRD 1284. *Possible Toxic Agents and Intermediates*, by M. S. Kharasch, University of Chicago, March 22, 1943. Div. 9-209-M5

4. OSRD 1504. *Thallium Compounds*, by Henry Gilman, Iowa State College, June 21, 1943. Div. 9-217-M1

5. OSRD 1792. *Fluorocarbons and Related Compounds*, Albert L. Henne, Ohio State University, September 10, 1943. Div. 9-232-M2
6. OSRD 3285. *The Toxicity of Compounds Containing Fluorine*, by Morris S. Kharasch, University of Chicago, February 21, 1944. Div. 9-350-M1
7. OSRD 3480. *Colorimetric Determination of Fluorine in Fluoro-organic Compounds*, by John H. Yoe and Lyle G. Overholser, University of Virginia, April 14, 1944. Div. 9-422.3-M1
8. OSRD 3481. *Determination of Fluorine in Fluoro-organic Compounds*, by John H. Yoe, Jason M. Salsbury, and James W. Cole, University of Virginia, April 14, 1944. Div. 9-422.3-M2
9. OSRD 3830. *The Determination of Fluorine in Fluoro-organic Compounds in Low Concentrations in Air*, by John H. Yoe, University of Virginia, June 27, 1944. Div. 9-422.3-M3
10. OSRD 4008. *The gamma-Fluorobutyrates and Related Toxic Compounds*, by Morris S. Kharasch, University of Chicago, July 11, 1944. Div. 9-231.32-M2
11. OSRD 4051. *Selenides*, by Charles D. Hurd, Northwestern University, August 22, 1944. Div. 9-214-M1
12. OSRD 4055. *The Toxicity of Compounds Containing Fluorine, II*, by Morris S. Kharasch, University of Chicago, August 22, 1944. Div. 9-350-M2
13. OSRD 4170. *Status Report on Toxicity and Vesicant tests of Compounds Referred to the University of Chicago Toxicity Laboratory, Through July, 1944*, by Hoylande D. Young, University of Chicago Toxicity Laboratory, October 3, 1944. Div. 9-300-M4
14. OSRD 4273. *A Summary of the Vapor Pressures and Volatilities of Compounds Studied at the University of Chicago Toxicity Laboratory up to August 1, 1944*, by C. Ernst Redemann, Saul W. Chaikin, Ralph B. Fearing, Drusilla Van Hoosen, Joseph Savit, Dora Benedict, George J. Rotariu, University of Chicago Toxicity Laboratory, November 4, 1944. Div. 9-200-M8
15. OSRD 4414. *Determination of Fluorine in Certain Fluoro-organic Compounds in Water*, by John H. Yoe, Jason M. Salsbury, and James W. Cole, University of Virginia, November 30, 1944. Div. 9-422.3-M4
16. OSRD 4629. *A Systematic Scheme for the Detection of Toxics on Plain Silica Tubes*, by D. Stanley Tarbell, R. B. Carlin, V. P. Wystrach, Erwin Klingsberg, J. F. Bunnett, and E. G. Lindstrom, University of Rochester, January 24, 1945. Div. 9-421.2-M2
17. OSRD 4843. *The Detection of Organic Fluorine Toxics. The Use of Thiocarbazones as Arsenical Detectors*, by Nathan L. Drake, University of Maryland, March 8, 1945 Div. 9-422.8-M14
18. OSRD 4981 *Effects of Methyl Fluoroacetate on Isolated Tissues and Enzyme Systems*, by Carl F. Cori, Sidney P. Colowick, Louis Berger, and Milton W. Slein, Washington University, June 2, 1945. Div. 9-351-M3
19. OSRD 5281. *Organic Compounds Containing Fluorine*, by Morris S. Kharasch, University of Chicago, June 28, 1945. Div. 9-232-M7
20. OSRD 5305. *Supplement to OSRD 4170, Status Report on Toxicity and Vesicant Tests of Compounds Referred to the University of Chicago Laboratory*, by R. K. Cannan et al, University of Chicago Toxicity Laboratory, July 5, 1945. Div. 9-300-M5
21. OSRD 5452. *Some Aspects of the Behavior of the Fluoroacetates and Fluoroethanol as Water Contaminants*, by Charles C. Price and William G. Jackson, University of Illinois, August 17, 1945. Div. 9-252.1-M2
22. OSRD 6054. *Preparation of Sodium Fluoroacetate, Compound 1080*, by Wilbur B. Reed, R. L. Jenkins, and E. E. Hardy, Monsanto Chemical Company, September 30, 1945. Div. 9-721.1-M1
23. OSRD 6062. *Ketenes*, by Charles D Hurd, Northwestern University, October 6, 1945. Div. 9-231.2-M1

OSRD INFORMAL REPORTS

24. Contract NDCrc-132, University of Chicago Toxicity Laboratory, E. M. K. Geiling, Inf. Month. Prog. Repts. on *Toxicity of Chemical Warfare Agents*, NDRC 9:3:1. Div. 9-125-M2
    a. No. 3, April 10, 1943.
    b. No. 6, July 10, 1943.
    c. No. 8, September 10, 1943
    d. No. 9, October 10, 1943.
    e. No. 10, November 10, 1943.
    f. No. 11, December 10, 1943.
    g. No. 12, January 10, 1944.
    h. No. 13, February 10, 1944.
    i. No. 14, March 10, 1944.
    j. No. 15, April 10, 1944.
    k. No. 16, May 10, 1944.
    l. No. 17, June 10, 1944.
    m. No. 18, July 10, 1944.
    n. No. 19, August 10, 1944.
    o. No. 20, September 10, 1944.
    p. No. 21, October 10, 1944.
    q. No. 22, November 10, 1944.
    r. No. 23, December 10, 1944.
    s. No. 24, January 10, 1945.
    t. No. 25, February 28, 1945.
25. Contract OEMsr-85, University of Nebraska, C. S. Hamilton, Inf. Month. Prog. Rept., October 1944.
26. Contract OEMsr-97, Iowa State College, Henry Gilman. Inf. Month. Prog. Repts.
    a. February 1943.
    b. November 1943.
27. Contract OEMsr-135, Northwestern University, Charles D. Hurd. Inf. Month. Prog. Repts.
    a. December 1943.
    b. March 1944.
    c. April 1944.
28. Contract OEMsr-313, The Rockefeller Institute for Medical Research, Max Bergmann and Joseph S. Fruton. Inf. Month. Prog. Rept., NDRC 9:3:1 No. 19, August 10, 1944.
29. Contract OEMsr-319, University of Rochester, D. Stanley Tarbell. Inf. Month. Prog. Rept., April 1944.
30. Contract OEMsr-391, University of Chicago, Morris S. Kharasch. NDRC 9:2:1 Inf. Rept. No. 6, *The Preparation of 2-Fluoroethyl Nitrosoalkylamides*, November 24, 1943. Div. 9-222.3-M1

31. Contract OEMsr-394, University of Chicago, Morris S. Kharasch. Inf. Month. Prog. Repts.
    a. April 1943.
    b. September 1943.
    c. October 1943.
    d. November 1944.

32. Contract OEMsr-532, Johns Hopkins University, Barnett Cohen. Inf. Month. Prog. Rept., NDRC 9:5:1 No. 18, July 10, 1944. Div. 9-255-M14

33. Contract OEMsr-549, E. I. duPont de Nemours & Co., Paul L. Salzberg. Inf. Month. Prog. Repts.
    a. December 1943.
    b. January 1944.

34. Contract OEMsr-556, New York University, Homer W. Smith. Inf. Month. Prog. Repts., NDRC 9:5:1. Div. 9-321.1-M17
    a. No. 20, September 10, 1944.
    b. No. 22, November 10, 1944.
    c. No. 26, April 10, 1945.
    d. No. 28, July 10, 1945.

35. Contract OEMsr-593, University of Illinois, Charles C. Price. Inf Month. Prog. Rept., April 1944. Div. 9-361-M2

36. Contract OEMsr-845, Monsanto Chemical Co., R. L. Jenkins. Inf. Month. Prog. Repts. Div. 9-252-M3 Div. 9-255-M15
    a. February 1944.
    b. March 1944.
    c. November 1944.
    d. January 1945.

37. Contract OEMsr-1050, New York University, R. K. Cannan and Milton Levy. Inf. Month. Prog. Repts., NDRC 9:5:1. Div. 9-387-M2
    a. No. 16, May 10, 1944.
    b. No. 18, July 10, 1944.

38. Contract OEMemr-57, University of Chicago, E. S. Guzman Barron.
    a. *On the Mechanism of Fluoroacetate Poisoning. Inhibition by Fluoroacetate of Fatty Acid Metabolism*, August 21, 1944. Div. 9-351-M1
    b. Bimonth. Prog. Rept. No. 19, October 4, 1944. Div. 9-351-M2
    c. Bimonth. Prog. Rept. No. 20, December 1, 1944. Div. 9-387-M4

39. Contract OEMemr-59, Johns Hopkins University, Curt P. Richter. *Recent Work on ANTU and Other Poisons*, May 18, 1945. (OSRD Insect Control Committee Report No. 78.) Div. 9-721-M2

40. Contract OEMemr-245, Cornell University Medical College, McKeen Cattell.
    a. Rept. No. 13, May 31, 1944. Div. 9-387-M3
    b. Rept. No. 14, July 31, 1944. Div. 9-526-M1
    c. Rept. No. 15, September 15, 1944. Div. 9-387-M3
    d. Rept. No. 22A, July 30, 1945. Div. 9-526-M1

41. Contracts OSRD M-3167 and M-4480, Fish and Wildlife Service, E. R. Kalmbach.
    a. Prog. Rept. No. 8, January 1, 1945.
    b. Prog. Rept. No. 9, April 1, 1945.
    c. Rept. No. 10, July 1, 1945.

MISCELLANEOUS

42. Memorandum on *Animal Poisons*, by Birdsey Renshaw to W. R. Kirner for transmission to R. Trelchler, Fish and Wildlife Service, December 30, 1943. Div. 9-721-M1

43. *A Summary of Fluorine Compounds Prepared or Examined in the United States to January 10, 1944*, by Marshall Gates, NDRC Division 9, February 17, 1944. Div. 9-252-M4

44. NDRC Division 9 Informal Memorandum No. 3. *Methyl Fluoroacetate (AF-1, MFA, TL551, T.1202)*, by Birdsey Renshaw, Marshall Gates, and Homer W. Smith, May 15, 1944. Div. 9-252.1-M1

45. Rodent Control Subcommittee of the OSRD Insect Control Committee, Minutes of Meetings.
    a. Second Meeting, November 30, 1944.
    b. Third Meeting, January 26, 1945.
    c. Fourth Meeting, March 30, 1945.
    d. Fifth Meeting, May 25, 1945.

46. Contract OEMsr-97, Iowa State College, Henry Gilman. Correspondence.
    a. August 4, 1942.
    b. December 16, 1943.

47. Contract OEMsr-394, University of Chicago, Morris S. Kharasch. Correspondence.
    a. February 8, 1943.
    b. February 18, 1943.
    c. December 15, 1944.

UNITED STATES ARMY REPORTS

Chemical Warfare Service

48. EATR 103. *Preparation and Physiological Action of bis(β-fluoroethyl)-sulfide*, January 22, 1934.

49. Med. Div. Rept. No. 6. *The Detection of Organic Fluorine Compounds in Water*, October 31, 1944.

50. Med. Div. Rept. No. 7. *Field Testing of Spot Test Procedure for Detection of Fluoro-organic Compounds in Water*, March 8, 1945.

51. MRL(EA) Rept. No. 19. *The Cardiac Actions of Methyl Fluoroacetate*, May 4, 1944.

52. TDMR 405. *1,2-Dichloro-1,2-difluoro-1,2-dinitroethane and 1-Chloro-1, 2,2-trifluoro-1,2-dinitroethane: Median Lethal Concentrations for Mice; Lacrimatory and Eye-irritant Actions on Man*, November 8, 1942.

53. TDMR 771. *Methyl Fluoroacetate*, November 19, 1943.

54. TDMR 772. *β-Fluoroethyl Alcohol*, November 19, 1943.

55. TDMR 887. *Identification of Agents Containing Fluorine: I. Use of Plain Silica Gel Tubes*, September 8, 1944.

56. CWS Monthly Progress Report on Insect and Rodent Control, No. 6, August 1945.

57. Med. Div. Inf. Month. Prog. Repts.
    a. December 15, 1944.
    b. April 15, 1945.
    c. June 15, 1945.

58. Medical Research Laboratory, Edgewood Arsenal. Inf. Month. Prog. Repts.
    a. September 15, 1943.
    b. October 15, 1943.
    c. November 15, 1943.
    d. December 15, 1943.

e. January 15, 1944.
f. February 15, 1944.
g. March 15, 1944.
h. April 15, 1944.
i. May 15, 1944.
j. June 15, 1944.
k. July 15, 1944.
l. August 15, 1944.

59. Contract W-49-057-CWS-23, University of Chicago Toxicity Laboratory. Inf. Month. Prog. Repts. on *Toxicity and Irritancy of Chemical Agents.*
a. No. N.S. 2, May 15, 1945.
b. No. N.S. 3, June 15, 1945.
c. No. N.S. 4, July 15, 1945.
d. No. N.S. 6, September 15, 1945.

MISCELLANEOUS

60. Report to the Commanding General, First Service Command, on *Field Test of Rodenticide — Sodium Fluoroacetate*, by R. F. Greeley, May 19, 1945.
61. *Field Tests of Rodenticide Sodium Fluoroacetate (Rodenticide 1080) on Wild Field Rodents*, by M. R. Pryor, Ninth Service Command, Fort Winfield Scott, California, June 14, 1945.
62. Memorandum to the Surgeon General, on *Rodenticide 1080, Sodium Fluoroacetate*, by R. N. Clark, June 25, 1945.
63. *Field Tests of Rodenticide Sodium Fluoroacetate on Camp Cooke Military Reservation*, by M. H. Buehler, Jr., August 1945.

UNITED STATES NAVY REPORTS

64. Fourteenth Naval District. Memorandum to the Bureau of Medicine and Surgery, on *Supplemental Report on Tests of "1080" in Rat Control*, by M. S. Johnson, March 28, 1945.
65. Memorandum to Island Command Medical Officer on *Trial Use of "1080" Rodenticide*, by T. B. Murray, April 12, 1945.
66. *Field Test Using 1080 Rodenticide at Navy One Forty and Navy One Three One*, by A. K. Crews, Malaria and Epidemic Control Unit, Navy 131, April 27, 1945.

UNITED STATES PUBLIC HEALTH SERVICE REPORTS

67. *Report on Chemical 1080*, by C. R. Eskey, Typhus Control Unit, U. S. Public Health Service, Atlanta, Georgia, May 9, 1945.
68. *Field Experiments During June, 1945, on the Use of Poisons 1080 and Anto, Conducted by U. S. Public Health Service Personnel Engaged in Typhus Control Activities*, by J. S. Wiley, Typhus Control Section, July 17, 1945.

UNITED STATES DEPARTMENT OF INTERIOR REPORTS

69. *Report of Test Baiting of Wharf Rats on Ogden City Garbage Dump, Using Sodium Fluoroacetate, Compound 1080*, by R. S. Zimmerman, Fish and Wildlife Service, June 29, 1945.
70. Quarterly Report, 4th Quarter, Fiscal Year, 1945, U. S. Dept. of the Interior, *Report of the Activities of the Wildlife Research Laboratory, Denver, Colorado*, by E. R. Kalmbach et al.

UNITED STATES—UNITED KINGDOM REPORTS

Project Coordination Staff (Edgewood Arsenal)

71. PCS Rept. No. 9. *Résumé of Recent Knowledge on the Technical Aspects of Chemical Warfare in the Field*, May 17, 1945.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

72. Porton Memorandum No. 15. *Classified List of Compounds Examined Physiologically Since 1940*, October 1941, and *Addendum 1*, June 4, 1945.
73. Porton Report No. 2544. *The Toxicology and Pharmacology of T.1202 in Animals, with Some Notes on Experimental Therapy and on Another Toxic Relation, T.1080*, September 23, 1943.
74. Porton Report No. 2549. *A New Titrimetric Method for the Estimation of Fluorine*, October 8, 1943.
75. Porton Report No. 2556. *The Estimation of Organic Fluorine Compounds. Part I. Methyl Fluoroacetate.* October 27, 1943.
76. Porton Report No. 2633. *The Toxicity of Methyl Fluoroacetate and Analogues*, July 17, 1944.
77. Ptn. 2643 (T.4161). *The Removal of Fluoroacetates from Water*, April 4, 1944.
78. Ptn. 4000 (T.5415). *Tabular Summary of Properties, Protection, etc., and Consideration on Alternate Charging in A C Weapons (Bombs and Spray) of Chemical Warfare Agents*, April 20, 1943.
79. Ptn. 4280 (T.9880). *Summary of Available Data on Compounds of Fluorophosphate and Fluoroacetate Types up to August 25, 1943.*
80. Ptn. 4280 (T.14339) and Y.18370. *Progress of Work on Fluoroacetates and Fluorophosphates: 1st Interim Report*, November 2, 1943.
81. Ptn. 4280 (T.16181). *The Detection of CW Agents Containing Fluorine: 2nd Interim Report*, December 4, 1943.
82. Ptn. 4280 (T.5007). *The Detection of CW Agents Containing Fluorine: 3rd Interim Report*, April 24, 1944.
83. Ptn. 4280 (T.9416). *The Detection of CW Agents Containing Fluorine: 4th Interim Report*, July 29, 1944.
84. Ptn. 4282 (T.4396A). *A Method for the Detection of Methyl Fluoroacetate in Dilute Aqueous Solution*, April 5, 1943.
85. Ptn. 4282 (T.5945). *Methyl Fluoroacetate and Its Analogues as Water Contaminants*, May 6, 1943.
86. Z.8170. *Storage of AF-1 and PF-1*, July 22, 1944.

Research Establishment, Sutton Oak

87. S.O. R 640. *Methyl Fluoroacetate and Related Compounds. Part I. Physicochemical Properties of Methyl Fluoroacetate*, February 3, 1943.

88. S.O. R 696. *An Improved Method for the Determination of Fluorine in Aliphatic Fluoro-Compounds and Fluorophosphates*, April 28, 1944.

89. S.O. R.701. *Methyl Fluoroacetate and Related Compounds. Part II. The Hydrolysis and Solubility of Methyl Fluoroacetate in Aqueous Solution*, January 27, 1944.

90. Y.18369. *Notes on Preparation of Methyl Fluoroacetate, Fluoroethyl Alcohol, and Diisopropyl Fluorophosphate*, December 20, 1943.

Extramural Research

91. Cambridge Extramural Testing Station (E. D. Adrian)

a. XZ.113 (W.14565 and Addendum W.15306). *Physiological Examination of Methyl Fluoroacetate. I*, by W. Feldberg, B. A. Kilby, and M. Kilby, November 14, 1942.

b. XZ.120 (W.18540). *Interim Report Upon the Physiological Examination of Methyl Fluoroacetate and Related Compounds*, by B. A. Kilby and M. Kilby, January 16, 1943.

c. XZ.124 (Y.2005). *Survey of Toxicities of Fluoroacetates and Related Compounds*, by B. A. Kilby and M. Kilby, March 25, 1943.

d. XZ.129 (Y.6516). *Physiological Examination of β-fluoroethyl Fluoroacetate*, by B. A. Kilby and M. Kilby, May 18, 1943.

e. XZ.130 (Y.7086). *A Note on the Volatility of Methyl Fluoroacetate*, by B. A. Kilby, June 4, 1945.

f. XZ.131 (Y.7833). *Second Survey of Toxicities of Fluoroacetates and Related Compounds*, by B. A. Kilby and M. Kilby, June 10, 1943.

g. XZ.142 (Y.16688). *Summary of work on the Treatment of Fluoroacetate and Fluorophosphate Poisoning. I*, by E. D. Adrian, K. J. Carpenter, and B. A. Kilby, November 15, 1943.

h. XZ.144 (Y.19499A). *Third Survey of Toxicities of Fluoroacetates and Related Compounds*, by K. J. Carpenter and B. A. Kilby, December 20, 1943.

i. XZ.145 (Y.19499B). *A Note on Chemical Constitution and Fluoroacetate-like Toxicity*, by K. J. Carpenter, B. A. Kilby, H. McCombie, and B. C. Saunders, January 8, 1944.

j. XZ.146 (Y.19500). *The Treatment of Methyl Fluoroacetate Poisoning*, by E. D. Adrian, K. J. Carpenter, and B. A. Kilby, January 8, 1944.

k. XZ.149 (Y.20197). *The Morbid Anatomy and Histology of Fluoroacetate Poisoning*, A. M. Barrett, January 14, 1944.

l. XZ.152 (Y.23096). *Fourth Survey of Fluoroacetates and Related Compounds*, by K. J. Carpenter and B. A. Kilby, March 6, 1944.

m. XZ.158 (Z.4979). *Treatment of Methyl Fluoroacetate Poisoning, Parts IV and V*, by K. J. Carpenter and B. A. Kilby, June 13, 1944.

n. XZ.159 (Z.6207). *A Note on the Detection and Recognition of Fluoroacetate Poisoning in Man*, by E. D. Adrian, K. J. Carpenter, and B. A. Kilby, June 30, 1944.

o. XZ.162 (A.9035). *Toxicity Examination of Various Compounds*, by K. J. Carpenter and B. A. Kilby, August 24, 1944.

p. XZ.163 (Z.9201). *Examination of Two Fluorine Analogues of the Nitrogen Vesicants*, by K. J. Carpenter and B. A. Kilby, August 31, 1944.

q. XZ.166 (Z.13120). *Toxicity and Excretion of AF-1 in the Cercopithecus Monkey*, by K. J. Carpenter and B. A. Kilby, November 10, 1944.

r. XZ.168 (Z.18348). *Toxicity Results – Part I. Fluoro-Carbon Compounds*, by K. J. Carpenter, February 20, 1945.

92. Cambridge University (H. McCombie)

a. *Report No. 1 on Fluoroacetates and Allied Compounds (W.16486). Methyl Fluoroacetate – Preliminary Report*, by H. McCombie, B. C. Saunders, R. V. A. Briscoe, and R. J. Enoleus, December 11, 1942.

b. *Report No. 2 on Fluoroacetates and Allied Compounds (W.20037)*, by H. McCombie and B. C. Saunders, February 17, 1943.

c. *Report No. 3 on Fluoroacetates and Allied Compounds (Y.2899). The Preparation of Fluoroethyl Alcohol*, by H. McCombie and B. C. Saunders, March 31, 1943.

d. *Report No. 4 on Fluoroacetates and Allied Compounds (Y.3697). β-Fluoroethyl Fluoroacetate*, by H. McCombie and B. C. Saunders, April 15, 1943.

e. *Report No. 5 on Fluoroacetates and Allied Compounds (Y.8850)*, by H. McCombie and B. C. Saunders, May 30, 1943.

f. *Report No. 6 on Fluoroacetates and Allied Compounds (Y.16056)*, by H. McCombie and B. C. Saunders, September 30, 1943.

g. *Report No. 7 on Fluoroacetates and Allied Compounds (Y.17980)*, by H. McCombie and B. C. Saunders, November 10, 1943.

h. *Report No. 8 on Fluoroacetates and Allied Compounds (Y.19184). β,β'-Difluoroethyl Ethylene Dithioglycol or Sesqui-Fluoro-H*, by H. McCombie and B. C. Saunders, November 30, 1943.

i. *Report No. 9 on Fluoroacetates and Allied Compounds (Y.19710). Quaternary Amines Containing Fluorine*, by H. McCombie and B. C. Saunders, January 1, 1944.

j. *Report No. 10 on Fluoroacetates and Allied Compounds (Z.8348)*, by H. McCombie and B. C. Saunders, July 14, 1944.

k. *Report No. 11 on Fluoroacetates and Allied Compounds (Z.13072)*, by H. McCombie and B. C. Saunders, August 8, 1944.

l. *Report No. 12 on Fluoroacetates and Allied Compounds (Z.13489)*, by H. McCombie and B. C. Saunders, November 10, 1944.

m. *Report No. 10 on Fluorophosphates and Allied Compounds (Y.5936)*, by H. McCombie and B. C. Saunders, May 22, 1943.

n. *Report No. 17 on Fluorophosphates and Allied Compounds (Y.20497)*, by H. McCombie and B. C. Saunders, December 31, 1943.

o. *Y.20351. Fluoroacetates Prepared and Examined at Cambridge up to December 31, 1943*, by H. McCombie and B. C. Saunders, January 20, 1944.

p. *Y.2084. Determination of Fluorine in Organic Compounds*, by H. McCombie and B. C. Saunders, December 31, 1943.

93. Strangeways Research Laboratory, Cambridge (H. B. Fell)
   a. Z.7188A. *Report on the Effect of Methyl Fluoroacetate and of Fluoroacetic Acid on Fibroblast Cultures*, by C. B. Allsopp and H. B. Fell, July 1944.
   b. Z.7188B *Report on the Effect of Methyl Fluoroacetate and of Methyl Chloroacetate on Cultures of Beating Embryo Chick Heart*, by C. B. Allsopp and H. B. Fell, July 1944.

94. Dyson Perrins Laboratory, Oxford University (R. Robinson). Robinson Research Report No. 122 (Z.4532). *β-β'-Difluorodiethylamine*, by A. W. Nineham, S. G. P. Plant, A. L. Thompsett, and R. Robinson, June 7, 1944.

95. Imperial College, London (H. V. A. Briscoe and H. J. Emeleus)
   a. W.20375. *Properties of Methyl Fluoroacetate*, by H. V. A. Briscoe and H. J. Emeleus, February 26, 1943.
   b. Y.3440. *The Analysis of Organic Fluoro Compounds: Modifications of the de Boer Zirconium-Alizarin Reagent*, by H. V. A. Briscoe and H. J. Emeleus, April 15, 1943.
   c. Y.7333. *The Analysis of Organic Fluorine Compounds, Part II*, by H. V. A. Briscoe and H. J. Emeleus, June 7, 1943.
   d. Y.8045. *The Hydrolysis of Fluoro Esters and the Preparation of Fluorohydrin*, by H. V. A. Briscoe and H. J. Emeleus, July 8, 1943.
   e. Y.13246 and correction Y.19361. *The Physical Properties of Various Fluoro Compounds in the Fluoroacetate Group*, by H. V. A. Briscoe and H. J. Emeleus, September 10, 1943.
   f. Y.16841. *The Detection of Volatile Fluorine-Containing Compounds*, by H. V. A. Briscoe and H. J. Emeleus, November 20, 1943.
   g. Z.12846. *Attempted Preparation of Fluoroacetic Acid or Its Esters from Various Starting Materials*, by A. Sporzynski and W. Kocay, October 26, 1944.

MISCELLANEOUS

96. Y.5682. *Report on Physiological Action of Methyl Fluoroacetate on Human Organism*, by A. Sporzynski, May 20, 1943.

97. Y.18709 and correction Y.19930. *Summary of British Work on Fluoroacetates and Fluorophosphates from August 25, 1943 to January 10, 1944.*

98. Y.10357. Chemical Board *Notes of the Informal Meeting of the Biochemical Subcommittee Held in Cambridge on July 1st 2nd, 1943.* August 17, 1943.

OPEN LITERATURE

99. Backer, H. J. and W. H. van Mels. *Vitesse de la Reaction des Acides Halogeno-carboxyliques et des Sulfites. II* Rev. Trav. Chim. **49**, 363-380 (1930).

100. Kalmbach, E. R. *'Ten-Eighty,' a War-Produced Rodenticide*. Science **102**, 232-233 (1945).

101. Swarts, F. *Contributions à l'étude des combinaisons organiques du fluor.* Mémoires couronnés et autres Mémoires publiés par l'Académie royale de Belgique **61** (1901).

102. Swarts, F. See *Über Difluoressigsäure*. Chem. Centralblatt, 1903, II, 709.

103. Swarts, F. Bull. Soc. Chim. Belg. **18**, 1134 (1906).

104. Swarts, F. *Sur l'alcohol monofluoré et la fluoracétine éthylenique*. Bull. sci. acad. roy. Belg., 1914, 7 17.

Chapter 11

OSRD FORMAL REPORTS

1. OSRD 314. *Preparation of Organometallic Compounds as Sources of Toxic Oxide Smokes and Flame Thrower Fuels*, by H. Gilman, Iowa State College, January 9, 1942. Div. 9-210-M1

2. OSRD 548. *Organo-Tin Compounds*, by H. Gilman, Iowa State College, May 2, 1942. Div. 9-216-M1

3. OSRD 846. *Preparation of Cadmium Salts and Organocadmium Compounds*, by H. Gilman, Iowa State College, August 26, 1942. Div. 9-215-M1

4. OSRD 868. *Toxicity and Vesicant Action of Various Organic Tin Compounds*, by E. M. K. Geiling and F. C. McLean, University of Chicago Toxicity Laboratory, September 7, 1942. Div. 9-316-M1

5. OSRD 1504. *Thallium Compounds*, by H. Gilman, Iowa State College, June 9, 1943. Div. 9-217-M1

6. OSRD 1517. *Organo Lead Compounds as Sternutators*, by H. Gilman, Iowa State College, June 16, 1943. Div. 9-218-M1

7. OSRD 4176. *Status Report on Toxicity and Vesicant Tests of Compounds Referred to the University of Chicago Toxicity Laboratory*, by Hoylande D. Young, University of Chicago Toxicity Laboratory, October 3, 1944. Div. 9-300-M4

8. OSRD 5305. *Supplement to OSRD 4176, Status Report on Toxicity and Vesicant Tests of Compounds Referred to the University of Chicago Toxicity Laboratory*, July 4, 1945. Div. 9-300-M5

OSRD INFORMAL REPORTS

9. Contract NDCrc-132. University of Chicago Toxicity Laboratory, E. M. K. Geiling, Inf. Month. Prog. Repts. on *Toxicity of Chemical Warfare Agents*. NDRC 9-4:1. Div. 9-125-M2
   a. No. 1, February 10, 1943.
   b. No. 2, March 10, 1943.
   c. No. 3, April 10, 1943.
   d. No. 4, May 10, 1943.
   e. No. 6, July 10, 1943.

UNITED STATES ARMY REPORTS

Chemical Warfare Service

10. *Field Laboratory Memorandum 1-45, Medical Division Status Summaries*, August 1944.

11. EATR 109. *Mouse Toxicity Data from January 1, 1933 to November 1, 1940 (Summary and Supplement 1)*, February 1, 1941.

12. MIT MR 139. *Performance of the M11 Canister against Carbonyls*, May 22, 1945.
13. TRLR 6. *Cadmium Oxide: Comparison of the Effectiveness of the Intimate Mix and Alloy 4-lb Toxic Incendiary Bombs*, October 25, 1943.
14. Flame Attack Studies, III. *The Lethal Effectiveness of Special Flame Thrower Fuels.* In preparation by the Medical Division, CWS. Number to be assigned.
15. TDMR 451. *Cadmium Oxide, Dispersion by Incendiary Bomb AN M54; Toxicity to Mice; Properties of Cadmium Oxide Smoke*, October 21, 1942.
16. TDMR 480. *Cadmium Oxide and Cadmium Chloride, Retention in the Respiratory Tract*, November 28, 1942.
17. TDMR 495. *Cadmium Oxide, Cadmium Chloride and Cadmium Nitrate*, December 5, 1942.
18. TDMR 503. *Cadmium Compounds, Toxicity, Pathology when Dispersed by Different Munitions*, December 23, 1942.
19. TDMR 519. *New Methods of Disseminating Chemical Agents, Cadmium Chloride Smoke from Burning-type Munition*, January 1, 1943.
20. TDMR 531. *Toxicity Data, A Status Report on the Development of War Gases at Edgewood Arsenal as of December 31, 1942*, January 10, 1943.
21. TDMR 532. *Cadmium Chloride, Toxicity and Pathology when Dispersed by a Grenade*, January 14, 1943.
22. TDMR 546. *The Use of Potassium Nitrate as an Oxidizing Agent in the Production of $CdCl_2$ Aerosols*, February 1, 1943.
23. TDMR 566. *Cadmium Fluoride, LC_{50} for Mice*, March 3, 1943.
24. TDMR 589. *Cadmium Oxide, Toxic Modifications of the AN-M50-A1 Bomb*, March 5, 1943.
25. TDMR 593. *Toxicity Data. A Status Report on the Development of War Gases at Edgewood Arsenal as of February 28, 1943*, March 11, 1943.
26. TDMR 620. *Toxicity Data. Status Report on the Development of War Gases at Edgewood Arsenal as of March 31, 1943*, April 9, 1943.
27. TDMR 629. *Selenium Dioxide, Toxicity of Smoke Dispersed Explosively*, April 16, 1943.
28. TDMR 650. *Toxicity Data. Status Report on the Development of War Gases at Edgewood Arsenal as of April 30, 1943*, May 10, 1943.
29. TDMR 654. *Cadmium Oxide, Toxic Modification of the AN-M50-A1 Bomb. Dispersion from Cd Mg Alloy Cases*, May 10, 1943.
30. TDMR 678. *Toxicity Data. Status Report on the Development of War Gases at Edgewood Arsenal as of May 31, 1943*, June 2, 1943.
31. TDMR 708. *Selenium Dioxide. Toxic Modification of Navy HE Projectiles, AP Projectiles*, December 1, 1943.
32. TDMR 873. *A Method for Analysis of Small Quantities of Selenium*, July 18, 1944.
33. TDMR 1007. *Selenium Dioxide Aerosol From Toxic Filled Capsules in AP Projectiles*, March 9, 1945.
34. TDMR 1079. *Selenium Dioxide Aerosol from Toxic Filled Capsules in HE Projectiles*, June 15, 1945.
35. MDR 38. *A Method for the Determination of Cadmium or Zinc*, June 15, 1945.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

36. Porton Departmental Report No. 189, *Metallic Carbonyls-Protection Afforded by Containers*, May 20, 1940.
37. Porton Memorandum No. 19, *Chemical Sampling of C. W. Agents in Field Experiments*, June 18, 1942.
38. Ptn. 3050 (T.15079) *Contamination of Water Supplies. Special Water Contaminants*, January 20, 1944.
39. Porton Red Book. Chemical Defence Research Department, *Report on the Chemistry and Toxicology of Certain Compounds*, May 25, 1940.

Extramural Research

40. Cambridge Extramural Testing Station (E. D. Adrian)
a. NZ.48 (V.1810). *The Toxicity of Cadmium Oxide Fumes T1151, Part 1: Concentration-Time Relationship for Rats*, by H. McCombie, B. A. Kilby, and Margaret Thacker, April 20, 1941.
b. ZN.57 (V.7583). *The Toxicity of Cadmium Oxide Fumes-T.1151*, by H. McCombie, B. A. Kilby, and Margaret Kilby, July 13, 1941.

MISCELLANEOUS

41. Chemical Board, *Physiological Sub-Committee, Meeting Held September 2, 1941. Notes F. 581-F. 592.*
42. Chemical Board, *Pure Chemical Sub-Committee, Notes H.293-H.303* (V.13015), October 16, 1941.
43. Chemical Board, *Meeting Held December 3, 1942. Notes P.983-P.989*, December 10, 1942.
44. No reference.
45. S.R.7 847 (V.10419). *Relative Toxicity of Cadmium Oxide and Phosgene for Monkeys*, by H. M. Barrett, September 5, 1941.

CANADIAN REPORTS

Experimental Station, Suffield, Alberta

46. Suffield Report No. 52. *A 4-lb Toxic Incendiary Bomb Containing Cadmium*, January 19, 1943.
47. Suffield Report No. 91. *Supplement to Suffield Report No. 52*, October 7, 1943.
48. Suffield Report No. 102. *Residual Pulmonary Fibrosis after Cadmium Compound Inhalation*, December 14, 1943.
49. Suffield Report No. 132. *Toxicity of Cadmium Oxide for Man*, June 10, 1945.
50. Technical Minute No. 25. *The Dispersion of Chemical Charges from Bofors Shell*, May 31, 1943.
51. Suffield Technical Minute No. 84. *Cadmium Compounds Applied Topically as Stimulants to Wound Healing*, February 19, 1945.
52. Suffield Technical Minute No. 100. *The Use of the Polarograph in the Analysis of Cadmium Aerosols*, June 23, 1945.
53. *Suffield Progress Notes for April 1943.*
54. C.E. 34. *Relative Toxicity of Cadmium Oxide and Phosgene for Monkeys*, University of Toronto, June 30, 1941.
55. C.E. 86. (Progress Report 7) *Precipitation of Cadmium Oxide Fumes. Stemming of 40 mm Q.F. A.A. Shell with Cadmatol*, University of Toronto, June 15 July 15, 1942.

56. C.E. 148. *Particle Size Distribution in Mechanically Dispersed Cadmium Oxide Smokes*, University of Toronto, March 6, 1944.
57. C.E. 148. *Particle Size Distribution in Mechanically Dispersed Cadmium Oxide and Chloride Smokes*, University of Toronto, July 21, 1944.
58. C.E. 152. *The Detection of Cadmium Oxide Particles in Lung Tissues*, University of Toronto, April 1944.
59. C.E. 183. *Detection of Cadmium Oxide in Rat Lung Tissues*, University of Toronto, September 21, 1944.
60. C.E. 200. *Toxicity and Pathology of the Inhalation of Cadmium Fumes*, University of Toronto, June 15, 1942.
61. C.E. 200. *Toxicity and Pathology of the Inhalation of Cadmium Fumes II*, University of Toronto, June 15, 1942.
62. C.P. 20. *Toxicity of Organic Cadmium Compounds*, University of Toronto, February 1, 1943.
63. C.P. 52. *The Detection of Cadmium Oxide in Sections of Mouse Lung*, University of Toronto, February 19, 1944.

Chemical Warfare Laboratories, Ottawa

64. Physiological Section Report No. 15. *Toxicity of Cadmium Salts of Nitrated Starch*, March 5, 1943.
65. Physiological Section Report No. 51. *H-Glycine Complex as a Therapeutic Agent in the Treatment of Cadmium Poisoning*, July 3, 1945.

OPEN LITERATURE

66. *History of Cadmium Poisoning and Uses of Cadmium*, L. Prohan, J. Ind. Hyg. Toxicol., **14**, 132, 174, 1932.
67. *Industrial Cadmium Poisoning*, F. M. R. Bulwer and H. E. Rothwell, Can. Pub. Health. J., January 1938.
68. *A Study of Cadmium Poisoning in Industry*, Public Health Reports, **57**, No. 17, April 24, 1942, U. S. Public Health Service.
69. *Selenium as a Potential Industrial Hazard*, H. C. Dudley, Public Health Reports, **53**, 281, 1938.
70. *The Toxicity of Nickel Carbonyl*, H. W. Armit, J. Hyg. **7**, 525, 1907; **8**, 565, 1908.
71. *The Toxicology of Carbonyls*, A. J. Amor, J. Ind. Hyg. Toxicol., **14**, 216, 1932.
72. *Nickel Carbonyl Poisoning*, W. W. Braudes, J. Am. Med. Assoc., 102, 1204, 1934.

Chapter 12

OSRD FORMAL REPORTS

1. OSRD 1563. *Pilot Plant Production of W*, by F. W. Blair and O. H. Alderks, The Procter and Gamble Company, July 2, 1943. Div. 9-241-M1
2. OSRD 4537. *Isolation of a Toxic Crystalline Protein from PGW*, by John H. Northrop and Moses Kunitz, The Rockefeller Institute for Medical Research, January 2, 1945. Div. 9-241-M2
3. OSRD 4651. *Immunochemical Studies on W*, by Michael Heidelberger and Elvin A. Kabat, Columbia University, February 2, 1945. Div. 9-525-M4
4. OSRD 4947. *The Preparation and Purification of Amorphous W*, by Alsoph H. Corwin, Sally H. Dicke, J. Gordon Erdman, Wilhelm R. Frisell, Bernice Pierson, Charlotte L. Karvel, Sylvia Lichter, and Joseph Walter, The Johns Hopkins University, April 25, 1945. Div. 9-241-M3
5. OSRD 4949. *The Bioassay of W*, by Alsoph H. Corwin, M. Virginia Carper, Sally H. Dicke, J. Gordon Erdman, Wilhelm R. Frisell, Charlotte L. Karvel, Sylvia Lichter, Mark Nickerson, Martha H. Pelletier, Bernice Pierson, and Joseph Walter, The Johns Hopkins University, November 8, 1945. Div. 9-341-M4
6. OSRD 4987. *The Analysis of Smokes*, by Henry E. Bent and Anna Jane Harrison, The University of Missouri, April 25, 1945. Div. 9-422.6-M2
7. OSRD 5033. *Effects of Toxic Doses of W on Blood Pressure, Blood Clotting, Blood Sugar, and Liver Glycogen in Rabbits and Rats, and Their Relationship to Certain Symptoms of W Poisoning*, by Carl F. Cori, Sidney P. Colowick, Louis Berger, and Milton W. Slein, Washington University, May 3, 1945. Div. 9-341-M1
8. OSRD 5437. *Consulting Work on W*, by Paul L. Salzberg, J. L. Keats, and F. C. McGrew, E. I. du Pont de Nemours and Company, August 11, 1945. Div. 9-241-M4
9. OSRD 5525. *The Toxicity of Various Preparations of W; A Comparison of Toxicities by Injection and by Inhalation*, by Morris A. Lipton, Lawrence S. Sonkin, Myrtle Bernstein, and Clarence C. Lushbaugh, University of Chicago Toxicity Laboratory, August 31, 1945. Div. 9-341-M2
10. OSRD 6131. *The Pathology of W*, by Homer W. Smith, Boris Krichesky, Val Jaeger, and William P. Anslow, Jr., New York University, October 17, 1945. Div. 9-341-M3
11. OSRD 6392. *Pilot Plant Preparation of Dispersible W*, by H. L. Craig and O. H. Alderks, The Procter and Gamble Company, January 7, 1946. Div. 9-241-M8
12. OSRD 6404. *The Preparation and Purification of Crystalline W*, by Alsoph H. Corwin and J. Gordon Erdman, The Johns Hopkins University, December 18, 1945. Div. 9-241-M5
13. OSRD 6435. *The Chemistry of the W-Bean Protein*, by Alsoph H. Corwin, Wilhelm R. Frisell, J. Gordon Erdman, and Bernice Pierson, The Johns Hopkins University, January 2, 1946. Div. 9-241-M6
14. OSRD 6437. *Chemical Properties of W Relating to Toxoid Preparation*, by Alsoph H. Corwin, Mark Nickerson, and J. Gordon Erdman, The Johns Hopkins University, January 3, 1946. Div. 9-241-M7
15. OSRD 6656. *The Preparation and Properties of Crystalline W*, by A. Benaglia, Milton Levy, and R. Keith Cannan, New York University, June 1, 1946. Div 9-241-M9

OSRD INFORMAL REPORTS

16. Contract OEMsr-313. The Rockefeller Institute for Medical Research, Max Bergmann. Inf. Month. Prog. Rept. January 10, 1944. Div. 9-124-M5
17. Contract NDCrc-132, University of Chicago Toxicity Laboratory, E. M. K. Geiling, Inf. Month. Prog. Repts. on *Toxicity of Chemical Warfare Agents*, NDRC 9:4:1 Div. 9-125-M2
    a. No. 15, April 10, 1944.
    b. No. 19, August 10, 1944.
    c. No. 20, September 10, 1944.

d. No. 21, October 10, 1944.
e. No. 23, December 10, 1944.
f. No. 25, February 28, 1945.

18. Contract OEMsr-901, Columbia University, Michael Heidelberger, Inf. Month. Prog. Repts. on *Immunochemical Studies*, NDRC 9-42. Div. 9-525-M4
a. No. 1, March 10, 1943
b. No. 2, April 10, 1943.
c. No. 3, May 10, 1943.
d. No. 4, June 10, 1943.
e. No. 5, July 11, 1943.
f. No. 6, August 10, 1943.
g. No. 7, September 10, 1943.
h. No. 8, October 10, 1943.
i. No. 9, November 10, 1943.
j. No. 10, December 10, 1943.
k. No. 11, January 10, 1944.
l. No. 12, February 10, 1944.
m. No. 13, March 10, 1944.
n. No. 14, April 10, 1944.
o. No. 15, May 10, 1944.
p. No. 16, June 10, 1944.
q. No. 17, July 10, 1944.
r. No. 18, August 10, 1944.
s. No. 19, September 10, 1944.
t. No. 20, October 10, 1944.
u. No. 21, November 30, 1944.

19. Contract OEMcmr-507 (continuation of OEMsr-901), Columbia University, Michael Heidelberger and Elvin A. Kabat. Div. 9-525-M4 Div. 9-525-M5
a. Inf. Month. Prog. Rept. No. 1 on *Immunochemical Studies*, April 1, 1945.
b. Inf. Month. Prog. Rept. No. 2 on *Immunochemical Studies*, June 1, 1945.
c. Final Rept. on *Immunochemical Studies on W*, by Michael Heidelberger, Elvin A. Kabat, Abner Wolf, and Ada E. Bezer, July 1, 1945.

MISCELLANEOUS

20. *Immunochemical Aspects of Protection Against W Poisoning*, by Birdsey Renshaw: minutes of meeting held at Dumbarton Oaks, 1703 32nd Street, N. W., Washington, D. C., on January 18, 1944. Div. 9-525-M2
21. *Notes on Conference on W Serology, Dumbarton Oaks*, June 10, 1944, by Birdsey Renshaw. Div. 9-525-M3

UNITED STATES ARMY REPORTS

Chemical Warfare Service

22. Medical Research Laboratory (Dugway Proving Ground) Rept. No. 2. *Studies of the Toxicity and Dispersibility of W in Munitions*, July 19, 1945.
23. Med. Div. Rept. No. 18, *A Test for the Detection of W in the Field*, December 27, 1944.
24. Chemical Warfare Monograph Volume 37. *Ricin*, September 30, 1918.
25. TDMR 699. *Preliminary Field Test on Powdered W Dispersed with the E5 Tail Ejection Bomb*, July 21, 1945.
26. TRLR 4, *Quantitative Determination of W by Hemagglutination*, September 21, 1943.
27. TRLR 5, *W: LC$_{50}$ for Mice. Effect of Prolonged Grinding on Toxicity. Toxicity and Immunization Studies with Monkeys. Hematology of Guinea Pigs*, September 21, 1943.
28. TRLR 10, *The Physiological Mechanism of W Action. The Toxicity of Special Preparations of W*, November 18, 1943.
29. Contract W-49-057-CWS-23. University of Chicago Toxicity Laboratory, Inf. Month. Prog. Repts. on *Toxicity and Irritancy of Chemical Agents.*
a. No. N.S. 4, July 15, 1945.
b. No. N.S. 5, August 15, 1945.
c. No. N.S. 6, September 15, 1945.
d. No. N.S. 7, October 15, 1945.
30. Contract W-18-035-CWS-884, The Johns Hopkins University, Inf. Month. Prog. Repts. on *Studies and Experimental Investigations in Regard to Preparation and Dispersion of W.*
a. No. 1, April 2, 1945.
b. No. 2, May 2, 1945.
31. Medical Research Laboratory (Edgewood Arsenal). Inf. Month. Prog. Repts.
a. September 15, 1943.
b. October 15, 1943.
c. November 15, 1943.
d. December 15, 1943.
e. January 15, 1944.
f. February 15, 1944.
g. March 15, 1944.
h. June 15, 1944.
i. July 15, 1944.
j. August 15, 1944.

UNITED STATES—UNITED KINGDOM REPORTS

Project Coordination Staff (Edgewood Arsenal)

32. PCS Rept. No. 9. *Résumé of Recent Knowledge on the Technical Aspects of Chemical Warfare in the Field*, May 17, 1945.

BRITISH REPORTS

33. *W, Summary of Results of Experiments to March, 1941*, by J. H. Gaddum, Physiological Section, March 25, 1941.
34. *The Chemical Properties of W*, by J. H. Gaddum. (Received June 15, 1942, by NDRC, Divisions 8-11).
35. *The Preparation of Aqueous "W" Paste and its Conversion to a Carbon Tetrachloride Suspension*, by R. T. Foster, Widnes Laboratory, Imperial Chemical Industries, Ltd., Rept. No. R GC 1324, May 21, 1943.
36. *Field Trials with W in Bombs*, by J. H. Gaddum. (Received May 25, 1943, by NDRC, Divisions 8-11).
37. Porton Memorandum No. 23. *The Value of W as a Charging for Chemical Weapons*, March 5, 1943.
38. Porton Report No. 2591. *Nasal Filtration of Droplets, Part I. The Penetration of Clouds of Fine Droplets through the Noses of Rats and Rabbits*, February 16, 1944.
39. *Part 2, Pathological Changes Produced in Small Laboratory*

Animals by W, by G. R. Cameron and Carleton, August 30 1940.

40. W (Undated summary of British work done during 1940-1942).

41. W 17850. *Notes on an Informal Meeting, held at 10 a.m. on 9th January 1943 at the Adelphi, to discuss W*, by C. L. Wheeler, January 14, 1943.

CANADIAN REPORTS

Experimental Station, Suffield, Alberta

42. Suffield Rept. No. 79. *Some Observations on the Biological Assay of W*, August 6, 1943.

43. Suffield Rept. No. 114. *The Efficiency of Dispersal and Casualty-Producing Power of Dry Powdered W*, June 10, 1944.

44. Suffield Rept. No. 116. *The Efficiency of Dispersal and Casualty-Producing Power of Dry Powdered W*, August 10, 1944.

45. Suffield Rept. No. 137. *The Efficiency of Dispersal of Agent W as a Dry Powder and from Suspension in Different Munitions*, June 30, 1945.

46. Suffield Rept. No. 145. *Dispersal and Physiological Effects of Agent "W" from Carbon Tetrachloride Suspension by the Type F HE Chem. Bomb*, November 5, 1945.

47. Suffield Technical Minute No. 14. *A Comparative Study of the Pathological Effects of American and British W in the Rat.* (Not dated and received on January 25, 1943 by NDRC, Divisions 8 11).

48. Suffield Technical Minute No. 45. *The Influence of Ball Milling on P & G W*, January 19, 1944.

49. Suffield Technical Minute No. 49. *Protection against W by Blockage or Partial Excision of the Reticuloendothelial Cell System in the Rat*, February 4, 1944.

50. Suffield Technical Minute No. 81. *The Comparative Dispersibility of W from Suspension and as a Dry Powder*, April 16, 1945.

Extramural Research

51. C.P. 62. *The Production of Aerosols of P.G. W*, by W. A. Bryce, University of Saskatchewan, July 1944.

52. C.P. 81. *The Mechanism of the Toxic Action of W in the Animal Body*, by W. Donald Graham, University of Toronto, May 1945.

Chemical Warfare Laboratories, Ottawa

53. Physiological Section Rept. No. 50. *The Immunological Behaviour of Some Fractions from Castor Beans*, May 14 1945.

OPEN LITERATURE

54. Beauvisage. Lyons, 1893. Paris, 1894.

55. Cushny, A. R. Arch f. exp. path. u. Pharm., 41, 439. *On ricin.*

56. Field, C. W. J. Exp. Med., **12**, 551, 1910. *A study of an extremely pure preparation of ricin.*

57. Flexner, S. J. Exp. Med., **2**, 197, 1897. *The histological changes produced by ricin and abrin intoxication.*

58. Foster, G. L. J. Biol. Chem., **55**, 383, 1923. *On carbohydrate metabolism.*

59. Foster, N. B. J. Biol. Chem., **7**, 379, 1909. *The influence of dietary factors on physiological resistance.*

60. Kobert, R. *Lehrbuch der intoxikationen* (1906).

61. Kraus, K. A. Diss. Johns Hopkins University (1941).

62. Michaelis, L. and Steindorff, K. Bioch. Z., **2**, 43, 1906. *The action of ricin on serum and on tissue cells in vitro.*

63. Ohmer, D. and Sauvan, A. Compt. rend. soc. biol., **68**, 638, 1910. *The action of solutions of abrin and of ricin on blood.*

64. Osborne, T. B. *The Vegetable Proteins.* Monographs on Biochemistry. Longmans, Green and Co., London, 1919.

65. Osborne, Mendel, and Harris. Amer. J. Physiol., **14**, 259, 1905. *The proteins of the castor bean with special reference to the isolation of ricin.*

66. Spies, Joseph R., E. J. Coulson and Henry Stevens, *The Chemistry of Allergens. X. Comparison of Chemical and Immunological Properties of CB-1A Preparations from Domestic Castor Beans and Brazilian Castor Bean Pomace.* J. Am. Chem. Soc., **66**, 1708–1709 (1944).

67. Spies, Joseph R., and E. J. Coulson, *The Chemistry of Allergens. VIII. Isolation and Properties of an Active Protein-polynucleotide Fraction, CB-1A, from Castor Beans*, J. Am. Chem. Soc., **65**, 1720–1725 (1943).

68. Stillmark, H. Arb. d. Pharmak. Inst. Dorpat., **3**, 58, 1889.

69. Wallbach G. Z. ges. exper. Med., 75, 378, 1931.

Chapter 13

OSRD FORMAL REPORTS

1. OSRD 3377. *N-Alkyl Carbamates of Aminophenols and Some Sulfur Containing Analogs*, by Elliot R. Alexander and Arthur C. Cope, Columbia University, July 11, 1944. Div. 9-222.1-M2

2. OSRD 3893. *Derivatives of Certain Dialkylaminophenyl-N-Methylcarbamates*, by Cliff S. Hamilton, University of Nebraska, July 13, 1944. Div. 9-222.2-M3

3. OSRD 4534. *m-Diethylaminophenyl-N-Methylcarbamate and Certain of Its Salts*, by C. S. Hamilton, E. J. Crogoe, R. J. Andres, Bill Elpern, and Robert F. Coles, University of Nebraska, January 2, 1945. Div. 9-222.2-M5

4. OSRD 4586. *Studies on the Preparation of Non-Volatile Toxic Agents*, by Karl Folkers, Richard F. Phillips, and Clifford H. Shunk, Merck and Co., Inc., January 17, 1945. Div. 9-229-M2

5. OSRD 4660. *N-Substituted Carbamates of Phenols Containing a Quaternary Ammonium Group. I. Derivatives of m-Dialkylaminophenols and 2-Methyl-5-Dialkylaminophenols*, by R. L. Shriner, J. C. Speck, Jr., C. R. Russell, and W. H. Elliott, Indiana University, February 5, 1945. Div. 9-222.4-M2

6. OSRD 4661. *N-Substituted Carbamates of Phenols Containing a Quaternary Ammonium Group. II. Derivatives of Thymol and Carvacrol*, by R. L. Shriner, J. C. Speck, Jr., C. R. Russell, and W. H. Elliott, Indiana University, February 5, 1945. Div. 9-222.4-M3

7. OSRD 4662. *The Synthesis of Toxic Carbamates of Amino-*

alcohols (Diaryl Homologs and Analogs), by L. Kaplan and C. R. Noller, Stanford University, February 5, 1945. Div. 9-222-M1

8. OSRD 4663. *Quaternary Salts of N-Alkylcarbamates of Aminophenols (Prostigmine Analogs)*, by C. D. Heaton, L. Kaplan, and C. R. Noller, Stanford University, February 5, 1945. Div. 9-222.4-M4
9. OSRD 4709. *N-Substituted Aryl Carbamates (III) and Related Miscellaneous Investigations*, by R. L. Shriner, J. C. Speck, Jr., William H. Elliott, and M. E. Synerholm, Indiana University, March 20, 1945. Div. 9-222-M2
10. OSRD 5003. *N-Alkyl Carbamates of 4-Substituted-3,5-Dimethylphenols*, by R. L. Shriner, C. R. Russell, and J. C. Speck, Jr., Indiana University, April 28, 1945. Div. 9-222.1-M3
11. OSRD 5017. *Derivatives of m-Alkylphenols (Quaternary Salts of Carbamate...)*, by Lee Irvin Smith, C. F. Koelsch, and Vaughn Engelhardt, University of Minnesota, May 1, 1945. Div. 9-222.4-M5
12. OSRD 5195. *Survey of Toxicities of Some 300 Aromatic Carbamates*, by William H. Elder, C. F. Failey, and B. E. Ginsburg, University of Chicago Toxicity Laboratory, August 22, 1945. Div. 9-322-M2
13. OSRD 5980. *Synthesis of Chemical Warfare Toxic and Vesicant Agents — Non-Volatile Toxic Agents — Preparation of the Methochloride of m-Diethylaminophenyl Methylcarbamate*, by P. L. Salzberg, W. A. Lazier, R. W. Hoyk, E. R. Alexander, D. C. England, E. K. Ellington, G. W. Rigby, and C. W. Todd, E. I. du Pont de Nemours & Company, February 12, 1946. Div. 9-222.2-M6
14. OSRD 6085. *The Preparation of Quaternary Salts of N-Methylcarbamates of Dialkylaminophenols*, by Homer Adkins, Harry P. Schultz, James E. Carnahan, E. Earl Royals, and A. L. Wilds, University of Wisconsin, December 1, 1945. Div. 9-222.4-M7
15. OSRD 6117. *The Pilot Plant Preparation of TL1217, TL1290 and Intermediates*, by R. L. Jenkins and E. E. Hardy, Monsanto Chemical Company, October 25, 1945. Div. 9-222.5-M7
16. OSRD 6353. *A Study of the Decomposition of the Carbamates of Certain Aminophenol Quaternary Salts*, by Paul D. Bartlett, Hyp J. Dauben, Jr., Sidney D. Ross, and Samuel Siegel, Harvard University, November 27, 1945. Div. 9-222.4-M6

MISCELLANEOUS

17. *Report on Toxic Substances*, by Edward Rogers and Karl Folkers, Merck and Company, Inc., October 30, 1942. Div. 9-300-M2
18. *Review of Carbamates Tested for Toxicity*, by Karl Folkers, Merck & Company, Inc., June 15, 1944. Div. 9-322-M1
19. *Progress Report on Carbamates*, by Henry Gilman, Iowa State College, April 2, 1946. Div. 9-222-M3

UNITED STATES ARMY REPORTS

Chemical Warfare Service

20. Medical Division Report No. 48. *Mode of Action of Substituted Carbamic Esters and a Comparison of Their Action on Acetylcholine Esterase Activity with That of Diisopropyl Fluorophosphate in Vivo and in Vitro*, August 28, 1945.
21. Contract W-49457-CWS-23, University of Chicago Toxicity Laboratory. Inf. Month. Prog. Repts. on *Toxicity and Irritancy of Chemical Agents.*
    a. No. N.S. 4, July 15, 1945.
    b. No. N.S. 5, August 15, 1945.
    c. No. N.S. 7, October 15, 1945.
    d. No. N.S. 8, December 15, 1945.
    e. No. N.S. 9, February 15, 1946.

BRITISH REPORTS

Extramural Research

22. Cambridge Extramural Testing Station.
    a. XZ.82 (V.16714). *Determination of the $I.D_{50}$ of Certain Quaternary Salts. VIII*, by H. McCombie, B. A. Kilby, and Margaret Kilby, November 26, 1941.
    b. XZ.84 (V.19416). *Determination of the $I.D_{50}$ of Certain Quaternary Salts. IX*, by H. McCombie, B. A. Kilby, M. Kilby, and B. C. Saunders, January 5, 1942.
    c. XZ.97 (W.1436). *Determination of the $I.D_{50}$ of Certain Tertiary and Quaternary Salts. XIII*, by H. McCombie, B. A. Kilby, and M. Kilby, April 10, 1942.
    d. XZ.151 (Y.23170). *Determination of the $I.D_{50}$ For Four Quaternary Salts. XVI*, by K. J. Carpenter and B. A. Kilby, February 16, 1944.

MISCELLANEOUS

23. W.A-1427-1a. *Professor Haworth's Compounds*, January 17, 1944.
24. W.4160. *Carbamates*, by R. D. Haworth, A. H. Lambert, and D. Woodcock, Sheffield, June 2, 1942.
25. Chemical Board Note H.245. *Professor Haworth's Compounds*, Pure Chemical Subcommittee Meeting held on December 9, 1940.

CANADIAN REPORTS

Chemical Warfare Laboratories, Ottawa

26. Research Section Report No.25, *Preparation of the Methiodide of the N-Methyl-Carbamic Ester of 2-Hydroxy-4-dimethylamino-Toluene*, by Leo Marion, August 4, 1943.
27. Research Section Report No. 32. *Synthesis of the Methiodide of 5-Methyl-3-Dimethylaminophenyl N-Methylcarbamate*, by Leo Marion, October 20, 1943.
28. Physiological Section Report No. 25. *Toxicity Tests of the Methiodide of 2-Methyl-5-Dimethylaminophenyl N-Methylcarbamate*, by S. F. Penny and J. F. Leib, November 1, 1943.
29. Research Section Report No. 34. *The Methiodides of m-Diethylaminophenyl N-Methylcarbamate and M-Diethylaminophenyl N-Phenylcarbamate*, by Leo Marion, November 22, 1943.

30. Physiological Section Report No. 31. *Toxicity Tests of the Methiodides of 3-Methyl-4-Dimethylaminophenyl N-Methylcarbamate and m-Diethylaminophenyl N-Methylcarbamate*, by S. F. Penny, January 4, 1944.
31. Research Section Report No. 36. *Synthesis of the Methiodide of 2,5-Dimethyl-4-Dimethylaminophenyl N-Methylcarbamate*, by Leo Marion, January 31, 1944.
32. Research Section Report No. 46. *Study of the Formation of the N-Methylcarbamate of 2-Methyl-5-Dimethylaminophenol and of m-Dimethylaminophenol*, by Leo Marion, November 14, 1944.
33. Development Section Report No. 104. *The Preparation of T.1708 from 2-Methyl-5-Dimethylaminophenol*, by J. Neil, A. K. Ames, R. V. Jackson, and E. A. Mellhinney, November 28, 1944.
34. Research Section Report No. 50. *Preparation of the Methiodides of N-Methylcarbamates of (a) Hydroxydialkylamino Derivatives of Diphenylmethane and (b) Hydroxyalkylamines*, by Leo Marion and O. E. Edwards, February 6, 1945.

Experimental Station, Suffield, Alberta

35. Suffield Report No. 89. *A Study of the Chemical and Toxicological Properties of a Quaternary Ammonium Salt*, by D. B. W. Robinson and D. D. Bonnycastle, September 21, 1943. Addendum to Suffield Report 89. *Some Improvements in the Synthesis of the N-Methylurethane of 6-Methyl 3-Dimethylamino-Phenol Methiodide*, by D. B. W. Robinson, December 10, 1943.
36. Technical Minute No. 47. *The Therapy of T. 1708 Poisoning in Rabbits*, by E. H. Davies, February 4, 1944.
37. Technical Minute No. 55. *Toxicity of Certain Urethane Derivatives*, by H. M. Barrett, April 15, 1944.
38. Technical Minute No. 71. *The Toxicity of Selected Urethane Derivatives as Determined by Intramuscular Implantation of Dry Material in Sheep*, by C. F. Failey and W. H. Elder, September 6, 1944.

Department of Pensions and National Health, Ottawa, Canada

39. C.P. 43. *Acute Toxicity Studies of 3-Methyl-4-Dimethylaminophenyl N-Methylcarbamate*, by M. G. Allmark and C. A. Morrell, December 1943.
40. C.P. 47. *Acute Toxicity Studies of 3-Methyl-5-Dimethylaminophenyl N-Methylcarbamate, The Effect of the Method of Injection on the Toxicity*, by M. G. Allmark and C. A. Morrell, January 1944.
41. C.P. 69. *Treatment of T.1708 Poisoning in Rats, Rabbits, and Dogs*, by M. G. Allmark and C. A. Morrell, September 1944.

OPEN LITERATURE

42. Stedman, Edgar and Barger, George. *Physostigmine (Eserine). Part III.* J. Chem. Soc., **127**, 247 (1925).
43. Stedman, Edgar. *Studies on the Relationship Between Chemical Constitution and Physiological Action. Part I. Position Isomerism in Relation to the Mitic Activity of Some Synthetic Urethanes.* Biochem. J., **20**, 719 (1926).
44. Stedman, Edgar. *The Isomeric Hydroxybenzyldimethylamines*, J. Chem. Soc., 1902 (1927).
45. Stedman, Edgar. *Studies on the Relationship Between Chemical Constitution and Physiological Action. Part II. The Mitic Activity of Urethanes Derived From The Isomeric Hydroxyphenyldimethylamines.* Biochem. J., **23**, 17 (1929).
46. Stedman, Edgar and Stedman, Ellen. *The Methylurethanes of the Isomeric α-Hydroxyphenylethyldimethylamines and Their Mitic Activity.* J. Chem. Soc., 609 (1929).
47. Stedman, Edgar and Stedman, Ellen. *The Methylurethanes of α-3-Hydroxy-4-methoxyphenylethyldimethylamine and α-4-Hydroxy-3-methoxyphenylethyldimethylamine and Their Mitic Activities.* J. Chem. Soc., 1126 (1931).
48. White, A. C. and Stedman, E. *The Physostigmine-like Action of Certain Synthetic Urethans.* J. Pharmacol., **41**, 259–88 (1931).
49. Aeschlimann, John A. and Reinert, Marc. *The Pharmacological Action of Some Analogs of Physostigmine.* J. Pharmacol., **43**, 413 (1931).
50. Aeschlimann, John A. *Poison for Animals Such as Rodents.* U. S. Patent 1,858,177, May 10, 1932 ((Chem. Abstr., **26**, 3888 (1932)).
51. Aeschlimann, John A. *Carbamic Acid Esters.* U. S. Patent 1,905,990, April 25, 1933 and British Patent 350,865, January 2, 1931 ((Chem. Abstr., **27**, 307 (1933)).
52. Aeschlimann, John A. *Disubstituted Carbamic Acid Esters of Phenols Containing a Basic Substituent.* U. S. Patent 2,208,485, July 16, 1940 ((Chem. Abstr., **35**, 136 (1941)).
53. Stevens, Joseph R. and Beutel, Ralph H. *Physostigmine Substitutes.* J. Am. Chem. Soc., **63**, 308 (1941).

Chapter 14

OSRD FORMAL REPORTS

1. OSRD-314. *Preparation of Organometallic Compounds as Sources of Toxic Oxide Smokes and Flame Thrower Fuels*, by Henry Gilman, Iowa State College, January 9, 1942. Div. 9-210-M1
2. OSRD-548. *Organo-Tin Compounds* by Henry Gilman, Iowa State College, May 2, 1942. Div. 9-210-M1
3. OSRD-810. *Screening Tests on Several Azine Compounds*, by E. M. K. Geiling and F. C. McLean, University of Chicago Toxicity Laboratory, August 18, 1942. Div. 9-324-M1
4. OSRD-831. *Synthesis of Compounds Related to Urushiol, Laccol, Rhengol and Thitsiol*, by R. L. Shriner, University of Indiana, August 28, 1942. Div. 9-243-M1
5. OSRD-840. *The Preparation of Mustard Gas and Certain of its Derivatives and Analogs*, C. S. Marvel and R. C. Fuson, University of Illinois, August 31, 1942. Div. 9-212.11-M2
6. OSRD-846. *Preparation of Cadmium Salts and Organocadmium Compounds*, Henry Gilman, Iowa State College, August 26, 1942. Div. 9-215-M1
7. OSRD-878. *Summary Report on Work Done on Chemical Warfare Problems at the University of Illinois*, C. S. Marvel and R. C. Fuson, University of Illinois, September 11, 1942. Div. 9-200-M2

8. OSRD-941. *The Sternutatory Properties of Certain Organic Compounds*, by Carl R. Noller, Stanford University, October 7, 1942. Div. 9-231.4-M1
9. OSRD-1017. *N-Vanillylundecylenamide and N-Vanillylmandelamide*, by Homer Adkins, University of Wisconsin, November 12, 1942. Div. 9-221.5-M1
10. OSRD-1030. *I. Rapid Methods for Synthesizing Certain War Gases. II. The Chemistry of the Sulfur Fluorides*, by J. H. Simons, Pennsylvania State College, October 21, 1942. Div. 9-200-M3
11. OSRD-1117. *The Preparation and Properties of Alkyl N-Nitroso-N-Alkycarbamates and Related Compounds* by M. S. Kharasch, University of Chicago, December 9, 1942. Div. 9-222.1-M1
12. OSRD-1284. *Possible Toxic Agents and Intermediates*, by M. S. Kharasch, University of Chicago, March 22, 1943. Div. 9-200-M5
13. OSRD-1294. *The Preparation of Ethyldichloroarsine and Related Compounds*, by M. S. Kharasch, University of Chicago, March 23, 1943. Div. 9-213.14-M5
14. OSRD-1356. *Synthesis of Some Basic Esters, Related to Choline and Its Derivatives*, by R. L. Shriner, Indiana University, April 21, 1943. Div. 9-231.1-M1
15. OSRD-1504. *Thallium Compounds* by Henry Gilman, Iowa State College, June 9, 1943. Div. 9-217-M1
16. OSRD-1517. *Organo Lead Compounds as Sternutators*, by Henry Gilman, Iowa State College, June 16, 1943. Div. 9-218-M1
17. OSRD-1529. *Preparation of Esters of α, α'-Dibromo or Dichloro Dibasic Acids*, by Homer Adkins, University of Wisconsin, June 22, 1943. Div. 9-231.1-M2
18. OSRD-1568. *I. The Preparation and Properties of Some Nitro-olefine Derivatives. II. The Determination of Vapor Pressures and Crystal Densities of Organic Compounds*, by M. L. Wolfrom, Ohio State University Research Foundation, July 3, 1943. Div. 9-227-M1
19. OSRD-2057. *The Preparation of Certain Nitrogen-Containing Compounds for Examination as CW Agents*, by M. L. Wolfrom, Stephen M. Olin, and E. E. Dickey, Ohio State University Research Foundation. Div. 9-229-M1
20. OSRD-3004. *Selenonium and Sulfonium Halides*, by C. D. Hurd, Northwestern University, January 1, 1944. Div. 9-219-M3
21. OSRD-3354. *I. Preparation of Compounds Other Than Nitrogen Mustards. II. Derivatives of CW Agents*, by George H. Coleman, Joseph E. Callen, Joseph J. Carnes, Chester M. McCloskey, Ronald E. Pyle, Gust Nichols, Frank A. Stuart, and Robert L. Sundberg, State University of Iowa, March 14, 1944. Div. 9-200-M6
22. OSRD-4051. *Selenides*, by Charles D. Hurd, Northwestern University, August 22, 1944. Div. 9-214-M1
23. OSRD-4175. *2-Chloroethylselenium Chloride, Selenium Oxychloride, 2-Chloroethaneseleninyl Chloride, and Ethaneseleninyl Chloride Hydrate*, by Charles D. Hurd, Northwestern University, September 29, 1944. Div. 9-214-M2
24. OSRD-4176. *Status Report on Toxicity and Vesicant Tests of Compounds Referred to the University of Chicago Toxicity Laboratory*, by Hoylande D. Young, E. M. K. Geiling, R. Keith Cannan, William Bloom, University of Chicago, October 3, 1944. Div. 9-300-M4
25. OSRD-4194. *The Preparation for Toxicity Tests of Some Heterocycles Containing a Nitrogen Atom Common to Two Fused Rings*, by C. R. Noller and L. Kaplan, Stanford University, September 27, 1944. Div. 9-224-M3
26. OSRD-4273. *A Summary of the Vapor Pressures and Volatilities of Compounds Studied at the University of Chicago Toxicity Laboratory*, by E. M. K. Geiling, et al., University of Chicago, November 4, 1944. Div. 9-200-M8
27. OSRD-4325. *The Preparation for Toxicity Tests of Some Ethylene and Acetylene Derivatives*, by C. D. Heaton, E. W. Torbohn, and C. R. Noller, Stanford University, November 9, 1944. Div. 9-234-M1
28. OSRD-4333. *Organic Arsenicals and Other Toxic Agents*, by C. S. Hamilton, E. J. Crague, Jr., R. J. Andres, Robert F. Coles, and Bill Ehrn, University of Nebraska, January 1, 1945. Div. 9-219-M4
29. OSRD-4662. *The Synthesis of Toxic Carbamates of Aminoalcohols (Dioxyl Homologs and Analogs)* by L. Kaplan and C. R. Noller, Stanford University, February 5, 1945. Div. 9-222-M1
30. OSRD-4700. *N-Substituted Aryl Carbamates (III) and Related Miscellaneous Investigations*, by R. L. Shriner, J. C. Speck, Jr., William H. Elliott, and M. E. Symonbolm, Indiana University, March 20, 1945 Div. 9-222-M2
31. OSRD-5003. *N-Alkyl Carbamates of ;-Substituted-3,5-Dimethylphenols*, by R. L. Shriner, C. R. Russell, J. C. Speck, Jr., Indiana University, April 28, 1945. Div. 9-222.1-M3
32. OSRD-5148. *Studies in the Synthesis of Organic Compounds of Sulfur, Nitrogen and Chlorine Which Possess Physiological Activity*, by R. C. Fuson, C. C. Price, and H. R. Snyder, University of Illinois, May 29, 1945. Div. 9-212.5-M4
33. OSRD-5194. *Tests for Vesicancy on Human Skin*, by E. M. K. Geiling, et al., University of Chicago, June 1, 1945. Div. 9-300-M3
34. OSRD-5247. *Paraphenylenediamine Compounds*, by Lee Irvin Smith, Vaughn Engelhardt, University of Minnesota, June 25, 1945. Div. 9-321.3-M1
35. OSRD-5305. *Supplement to OSRD-4176, Status Report on Toxicity and Vesicant Tests of Compounds Referred to the University of Chicago Toxicity Laboratory*, E. M. K. Geiling, et al., University of Chicago, July 4, 1945. Div. 9-300-M5
36. OSRD-5502. *Synthesis of Chemical Warfare Toxic and Vesicant Agents Carbon Monoxide Pentamer*, by D. C. England, B. W. Howk, P. L. Salzberg, F. I. du Pont de Nemours and Company, September 7, 1945. Div. 9-233 M1
37. OSRD-5980. *Synthesis of Chemical Warfare Toxic and Vesicant Agents – Nonvolatile Toxic Agents – Preparation of the Methochloride m-Diethylaminophenyl Methylcarbamate*, by P. L. Salzberg, W. A. Lazier, B. W. Howk, E. R. Alexander, D. C. England, E. K. Ellington, G. W. Rigby, and C. W. Todd, E. I. du Pont de Nemours and Company, February 12, 1946. Div. 9-222.2-M6
38. OSRD-6062. *Ketenes*, by Charles D. Hurd, Northwestern University, October 6, 1945. Div. 9-231.2-M1

39. OSRD-4000. *The Preparation of Miscellaneous Chemical Warfare Agents*, by Homer Adkins, John E. Castle, Robert J. Gander, Warren D. Niederhauser, E. Earl Royals, and A. L. Wilds, University of Wisconsin, December 1, 1945. Div. 9-200-M11

OSRD INFORMAL REPORTS

40. Contract OEMsr-97, Iowa State College, Henry Gilman. Inf. Month. Prog. Repts. Div. 9-122-M1
    a. December 1941 Div. 9-122-M2
    b. January 1942.
    c. February 1942.
    d. April 1942.
    e. May 1942.
    f. June 1942.
    g. July 1942.
    h. August 1942.
    i. September 1942.
    j. March 1943.
    k. June 1943.
    l. July 1943.
    m. August 1943.
    n. September 1943.
    o. October 1943.
    p. November 1943.
    q. December 1943.
    r. January 1944.
    s. March 1944.
41. Contract OEMsr-134, University of Virginia, John H. Yoe, Inf. Month. Prog. Repts.
    a. June 1943. Div. 9-422.7-M3
    b. February 1944
42. Contract OEMsr-135, Northwestern University, Charles D. Hurd, Inf. Month. Prog. Repts.
    a. May 10, 1944. Div. 9-123-M1
    b. June 10, 1944.
    c. Informal Report dated November 23, 1945.
    d. " " " November 30, 1945.
43. Contract OEMsr-136, Stanford University, C. R. Noller. Inf. Month. Prog. Rept. dated June 1944. Div. 9-222.2-M2
44. Contract OEMsr-161, The Ohio State Research Foundation, M. L. Wolfrom. Inf. Month. Prog. Repts. Div. 9-255-M10
    a. May 10, 1943.
    b. June 10, 1943.
    c. July 10, 1943.
    d. NDRC 9:2:1 Inf. Rept. No. 3. *Preparation of Some Derivatives of d-Camphor*, July 13, 1943. Div. 9-242-M1
    e. NDRC 9:2:1 Inf. Rept. No. 7. *The Preparation of d-Camphor Oxime and Isonitroso-d-Camphor*, November 24, 1943. Div. 9-242-M2
45. Contract OEMsr-195, Indiana University, R. L. Shriner. Inf. Month. Prog. Rept. dated March 1943. Div. 9-255-M8
46. Contract OEMsr-223, State University of Iowa, George H. Coleman. Inf. Month. Prog. Repts. Div. 9-600-M1 Div. 9-255-M13
    a. April 1944.
    b. July 1944.
    c. August 1944.
47. Contract OEMsr-300, University of Illinois, R. C. Fuson. Inf. Month. Prog. Repts. Div. 9-312.11-M10
    a. September 1942.
    b. February 1943.
    c. September 1944.
    d. October 1944.
    e. NDRC 9:2:1 Inf. Rept. No. 1. *Halonitroso Compounds*, March 27, 1943. Div. 9-228-M1
    f. NDRC 9:2:1 Inf. Rept. No. 2. *The Preparation of o-Cyanophenacyl Chloride*, May 10, 1943. Div. 9-223.3-M1
48. Contract OEMsr-372, University of Minnesota, Lee I. Smith. NDRC 9:2:2 Inf. Rept. No. 3. *Acrylonitrile and Related Compounds*, June 22, 1943. Div. 9-225-M1
49. Contract OEMsr-394, University of Chicago, Morris S. Kharasch. Inf. Month. Prog. Repts. Div. 9-211.4-M2
    a. June 1942.
    b. September 1942.
    c. January 1943.
    d. February 1943.
    e. March 1943.
    f. April 1943.
    g. May 1943.
    h. June 1943.
    i. July 1943.
    j. August 1943.
    k. October 1943.
    l. December 1943.
    m. February 1944.
    n. March 1944.
    o. April 1944.
    p. May 1944.
    q. July 1944.
    r. August 1944.
50. Contract OEMsr-1124, Merck and Company, Karl Folkers. Inf. Month. Prog. Repts. Div. 9-255-M12
    a. October 10, 1943.
    b. November 10, 1943.

UNITED STATES ARMY REPORTS

51. University of Chicago Toxicity Laboratory. Inf. Month. Prog. Rept. N.S. 6, September 15, 1945.
52. CWS Monthly Progress Report on Insect and Rodent Control No. 6, August 1945.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

53. Porton Memorandum No. 15. *Classified List of Compounds Examined Physiologically Since 1915. Addendum I. Includes all Compounds Examined at Porton and Cambridge from September 1941 to February 1945*, October 1941.
54. C.D. Report No. 1076. *Chemical, Physical and Physiological Properties of Certain Volatile Fluorine Compounds*, March 3, 1941.

Extramural Research

55. Cambridge Extramural Testing Station (E. D. Adrian)
    a. XZ.30 (U.20180A). *Examination of Four Trialkyl Lead Sulphonamide Derivatives*, by H. McCombie, B. C. Saunders, B. A. Kilby, and Margaret Thacher, December 13, 1941.
    XZ.31. *Determination of the L.D.₅₀ (Mice) of Certain Quaternary Salts (VII)*, by H. McCombie, B. A. Kilby, and Margaret Thacher, January 4, 1940.
    XZ.32. *Examination of di(β-Chloroethyl) Methylamine Hydrochloride*, by H. McCombie, B. A. Kilby, and Margaret Thacher, December 31, 1940.
    XZ.33 *Statement on the Seventh Month's Work*, by H. McCombie, B. A. Kilby, and Margaret Thacher, January 8, 1941.
    b. XZ.81 (V.16087). *The Physiological Examination of Dichloro and Dibromoformoxime*, by H. McCombie, B. A. Kilby, Margaret Kilby, and B. C. Saunders, November 23, 1941.
    c. XZ.144 (Y.10409A). *Third Survey of Toxicities of Fluoroacetates and Related Compounds*, by K. J. Carpenter and B. A. Kilby, December 20, 1943.
    d. XZ.154 (Y.23006). *Examination of Dimethylamino-sulphuryl Chloride and Fluoride*, by K. J. Carpenter and B. A. Kilby, March 6, 1944.
    e. XZ.162 (Z.9035). *Toxicity Examination of Various Compounds*, by K. J. Carpenter and B. A. Kilby, August 24, 1944.

56. Cambridge University (H. McCombie)
    a. V.1307. *Interim Report on Toxic Lead Compounds. Report No. 10*, by H. McCombie and B. C. Saunders, April 22, 1941.
    b. V.5829. *1. Preparation of Toxic Lead Compounds of the Type R·SO₂NR'PbR'₂. 2. Preparation of Aryl Lead Salts. 3. Preparation of Some Organic Tin Compounds. 4. (a) Preparation of Thallium Compounds of the Type R₂TlX. (b) Preparation of Mercury Compounds of the Type RHgX. (c) Preparation of Toxic Bismuth Compounds. (d) Diphenyl Antimonious Acetate*, by H. McCombie and B. C. Saunders, June 28, 1941.
    c. V.15071. *Preparation of Dichloralimethyl Ether, Dimethyl Fluorophosphate, and Dichloroformaldoxime*, by H. McCombie and B. C. Saunders, October 31, 1941.
    d. XZ.66 (V.1338718). *Physiological Tests on Five Organo-Bismuth Compounds*, by E. D. Adrian, H. McCombie, B. C. Saunders, B. A. Kilby, and Margaret Kilby, December 30, 1941.
    e. (Y.15030). *Report No. 6 on Fluoroacetates and Allied Compounds*, by H. McCombie and B. C. Saunders, September 30, 1943.

57. Imperial College of Science and Technology (H. V. A. Briscoe)
    (W.9015). *Provisional Assessment of the Value of Fluorine Compounds as C.W. Agents*, by H. V. A. Briscoe and H. J. Emeleus, September 2, 1942.

58. Imperial College, London (I. M. Heilbron).
    (V.10707). *The Bromination of Methyl n-Propyl Ketone*, by I. M. Heilbron, E. R. H. Jones, J. R. Catch, G. Rose, and W. Wilson, January 21, 1942.

MISCELLANEOUS

59. Porton Red Book. Chemical Defence Research Department, *Report on the Chemistry and Toxicology of Certain Compounds*, May 25, 1940.

CANADIAN REPORTS

60. Research Section Note No. 32. *Stability of Dichloroformoxime (Phosgene Oxime) in Various Solvents*, by J. W. Dale, June 17, 1944.

OPEN LITERATURE

61. L. Birckenbach and K. Sennewald, *Über Pseudohalogene XV*, Ann., **490**, 7-30 (1931).
62. Günther Endres, *Über die Einwirkung von Halogenen auf Knallquecksilber*, Ber., **65**, 65-69 (1932).
63. H. Mohler, Synthesis and Properties of the Nettle Gases, Protar, **7**, 37-50 (1941).
64. Wilhelm Prandtl and Werner Dellfuss, *Über das Chlornitroso-methan, das Dichlor-formoxim (Phosgen-oxim) und einige ihrer Derivate, 2. Mitteil.: Über zwei neue Derivate der Kohlensäure*, Ber., **65**, 754-759 (1932).
65. Sartori, Mario. *The War Gases*, New York, D. Van Nostrand Company, Inc., (1939).
66. U.S.P. 2,200, 742. *Process for Preparation of Phosgene Oxime*, P. J. Ehmann and W. O. Walker to Amul Chemical Company of Marinette, Wis., October 27, 1942.

Chapter 15

OSRD FORMAL REPORTS

1. OSRD 155. *Analysis of Inhomogeneous Smoke*, by V. K. LaMer and David Sinclair, Columbia University, November 5, 1941. Div. 10-501.11-M1
2. OSRD 364. *Report on Production of Smokes of Homogeneous Particle Size for Screening Tests and Development of Dyes from Thermally Dispersed Smokes*, by V. K. LaMer, Columbia University, January 20, 1942. Div. 10-501.11-M3
3. OSRD 1668. *A Portable Optical Instrument for the Particle Sizes in Smokes, the "Owl", and an Infrared Homogeneous Aerosol Generator*, by V. K. LaMer and David Sinclair, Columbia University, August 24, 1943. Div. 10-501.11-M6
4. OSRD 3944. *A Vapor Train Study of the Comparative Vesicancy of Mustard and Several Related Amines and Sulfides on Human Skin*, by Simon Black, Kenneth P. DuBois, and Morris A. Lipton, University of Chicago Toxicity Laboratory, August 30, 1944. Div. 9-361.1-M1
5. OSRD 4176. *Status Report on Toxicity and Vesicant Tests of Compounds Referred to the University of Chicago Toxicity Laboratory*, by Hoylande D. Young, University of Chicago Toxicity Laboratory, October 3, 1944. Div. 9-300-M4
6. OSRD 4947. *Preparation and Purification of Amorphous W*, by Alsoph H. Corwin, Sally H. Dicke, J. Gordon Erdman, Wilhelm R. Feisel, Bernice Pierson, Charlotte L. Karel, Sylvia Lichter, and Joseph Walter, April 25, 1945. Div. 9-241-M3

7. OSRD 5032. *A Formal Analysis of the Action of Liquid Vesicants on Bare Skin*, by Herbert D. Landahl, University of Chicago Toxicity Laboratory, May 5, 1945. Div. 9-300-M2
8. OSRD 5160. *Observations on the Role of Water in the Susceptibility of Human Skin to Vesicant Vapors*, by Birdsey Renshaw, June 1, 1945. Div. 9-361.1-M4
9. OSRD 5194. *Tests for Vesicancy of Human Skin to January 1, 1945*, by John F. Thomson, Hoylande D. Young, Joseph Savitt, Eugene Goldwasser, Raymond G. Murray, and Peter DeBruyn, University of Chicago Toxicity Laboratory, June 1, 1945. Div. 9-300-M3
10. OSRD 5195. *Survey of Toxicities of Some 300 Aromatic Carbamates*, by William H. Elder, C. F. Failey, and B. E. Ginsburg, University of Chicago Toxicity Laboratory, August 22, 1945. Div. 9-322-M2
11. OSRD 5305. *Supplement to OSRD 4176, Status Report on Toxicity and Vesicant Tests of Compounds Referred to the University of Chicago Toxicity Laboratory*, University of Chicago Toxicity Laboratory, July 4, 1945. Div. 9-300-M5
12. OSRD 5525. *Toxicity of Various Preparations of W: A Comparison of Toxicities by Injection and by Inhalation*, by Morris A. Lipton, Lawrence Sonkin, Myrtle Bernstein, and Clarence C. Lushbaugh, University of Chicago Toxicity Laboratory, August 31, 1945. Div. 9-341-M2

OSRD INFORMAL REPORTS

13. Contract NDCrc-132, University of Chicago Toxicity Laboratory. Informal Monthly Progress Reports on Toxicity of Chemical Warfare Agents: Div. 9-125-M2
    a. NDRC 9:4:1 No. 5, June 10, 1943.
    b. NDRC 9:4:1 No. 10, November 10, 1943.
    c. NDRC 9:4:1 No. 12, January 10, 1944.
    d. NDRC 9:4:1 No. 13, February 10, 1944.
    e. NDRC 9:4:1 No. 14, March 10, 1944.
    f. NDRC 9:4:1 No. 15, April 10, 1944.
    g. NDRC 9:4:1 No. 16, May 10, 1944.
    h. NDRC 9:4:1 No. 17, June 10, 1944.
    i. NDRC 9:4:1 No. 18, July 10, 1944.
    j. NDRC 9:4:1 No. 20, September 10, 1944.
    k. NDRC 9:4:1 No. 22, November 10, 1944.
    l. NDRC 9:4:1 No. 23, December 10, 1944.
    m. NDRC 9:4:1 No. 24, January 10, 1945.
14. Contract OEMsr-102. NDRC Munitions Development Laboratory, University of Illinois, H. F. Johnstone. Monthly Progress Reports: Div. 9-10-M3
    a. August 1944.
    b. August 1945.
15. Contract OEMsr-148. Columbia University, Victor K. LaMer. Informal Report No. 10.2-15, *The Slope-O-Meter: An Instrument for the Rapid Determination of Particle Radius and Concentration in the Laboratory and Field*, June 19, 1944. Div. 9-414.1-M1

UNITED STATES ARMY REPORTS

Chemical Warfare Service

16. TDMR 616. *Possible Chemical Warfare Agents of the Axis Powers*, April 26, 1943.
17. Contract W-49-057-CWS-23. University of Chicago Toxicity Laboratory Report No. 56, *Effects of Temperature, Humidity, and Season on the Reactions of Human Skin to Mustard Vapor*, by John C. Troxel and John Thomson, November 30, 1945.
18. Contract W-49-057-CWS-23, University of Chicago Toxicity Laboratory Informal Monthly Progress Reports on *Toxicity and Irritancy of Chemical Agents.*
    a. No. N.S. 2, May 15, 1945.
    b. No. N.S. 3, June 15, 1945.
    c. No. N.S. 4, July 15, 1945.
    d. No. N.S. 5, August 15, 1945.
    e. No. N.S. 6, September 15, 1945.
    f. No. N.S. 7, October 15, 1945.
    g. No. N.S. 8, December 15, 1945.
    h. No. N.S. 9, February 15, 1946.
    i. No. N.S. 10, April 15, 1946.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

19. Chemical Warfare Pocket Book — H.M.S.O., 1942.
20. Porton Memorandum No. 25. *The Sampling and Analysis of Initial Clouds*, October 7, 1943.
21. Porton Report No. 2282. *Record of Work Done and Results Attained with Glass Bombs Mk. I and II*, October 1, 1941.
22. Porton Report No. 2397. *The Production of Particulate Clouds from Bombs. Part II. Comparison of Different Thickness of Burster and Case*, July 18, 1942.
23. Porton Report No. 2463. (*1*) *The Cascade Impactor: An Apparatus for Sampling Solid and Liquid Particulate Clouds.* (*2*) *Addendum 1. Some Improvements in the Cascade Impactor*, September 10, 1943.
24. Porton Report No. 2482. *Dispersion of Particulate Suspensions from 250 lb. H.E./Chem. Bombs Dropped from High Altitude and Burst at Rest*, February 25, 1943.
25. Porton Report No. 2507. *Drop Trap Methods for the Chemical Sampling of Initial Clouds*, August 20, 1943.
26. Porton Report No. 2561. *Toxicity of Particulate Clouds of HN3 and H*, January 28, 1944.
27. Porton Report No. 2562. *Toxicity of HN3 in Droplet Form*, November 17, 1943.
28. Porton Report No. 2591. *Nasal Filtration of Droplets. Part I. The Penetration of Clouds of Fine Droplets through the Noses of Rats and Rabbits*, February 16, 1944.
29. Porton Report No. 2600 (Y.23339). *Nasal Filtration of Droplets*, February 16, 1944.
30. Porton Report No. 2613 (Z.1168). *The Application of Characterizers to the Estimation of Cloud Samples on Cascade Impactor Plates*, April 20, 1944.
31. Ptn. 1502/5 (T.22634). *Calculation of Impaction Efficiency*, 1943.
32. Ptn. 1600 (T.11404). *Methods of Obtaining Size Distributions from Cascade Impactor Plates without the Microscope*, September 1, 1943.
33. Ptn. 1600 (U.3998). *Instructions for the Use of Cascade Impactor*, April 1, 1944.
34. Ptn. 1601/2 and Addenda (S.6117A) (S.8990) (S.8953A). (*1*) *The Chemical Selector.* (*2*) *Addendum.* (*3*) *The Particle Size Cut-Off in the Chemical Selector*, June 10, 1942.

35. Ptn. 1708 (S.2507). *Experiments on Particulate Clouds*, February 28, 1943.
36. Ptn. 1708 (T.12258). *Sampling of Particulate Clouds with Impingers*, October 25, 1943.

Research Establishment, Sutton Oak

37. S.O./R 588. *Life Time of Spherical Drops of the Commoner Vesicants, Lachrymators and Sternutators*, March 21, 1942.

CANADIAN REPORTS

Experimental Station, Suffield, Alberta

38. Suffield Report No. 52. *A 4 lb. Toxic Incendiary Bomb Containing Cadmium*, January 19, 1943.
39. Suffield Report No. 145. *Field Experiments with W Suspensions*, November 5, 1945.

Extramural Research

40. C.E. 86. *Precipitation of Cadmium Oxide Fumes*, by G. F. Wright and E. Simmons, July 15, 1942.
41. C.E. 209. *Toxicity and Pathology of the Inhalation of Cadmium Fumes*, by D. Irvin and E. Simmons, June 15, 1943.

OPEN LITERATURE

42. Dallavalle, J. M. — *Micromeritics: the Technology of Fine Particles*, Pitman Company, New York, 1943, xiv + 428 pp.
43. Fairs, G. L. — *The Use of the Microscope in Particle Size Analysis*. Chemistry and Industry **62**, 374–378 (1943).
44. Heywood, H. — *The Measurement of Particle Size*. Proc. Institution of Mech. Engineers (London) **160**, 257–347 (1938).
45. Landahl, H. D. — *The Use of Wires in Assessment of Aerosols*. In press. (University of Chicago, 1945.)
46. Sell, W. — *Staubausscheidung an einfachen Körpern und in Luftfiltern*. Forschungsheft **347**, 1–23 (1931).
47. Whytlaw-Gray, R. — (1) *Disperse Systems in Gases*. Trans. Faraday Soc. **32**, 1042–1047 (1936). (2) *Ibid.* p. 1073–1084 (by H. Watson).
48. Winkel, A. and H. Wilmann. *Die Messung der Wärmebewegung an Aerosolen und Ihre Verwendung zur Trilchen grössenbestimmung*. Z. Electrochemie **46**, 181–185 (1940).

Chapter 16

OSRD FORMAL REPORTS

1. OSRD 580. *Constant-Flow Micro-Apparatus for Exposure of Mice to Volatile Toxic Agents under Controlled Conditions*, by J. O. Hutchens, University of Chicago Toxicity Laboratory, May 20, 1942. Div. 9-372-M2
2. OSRD 683. *A Method for Delivering Equal Amounts of Fluids of Differing Physical Properties*, by Philip D. McMaster, The Rockefeller Institute for Medical Research, July 10, 1942. Div. 9-371-M2
3. OSRD 800. *Toxicity and Incidence of Lipid Pneumonia upon Inhalation of Automobile Oil (S.A.E. #10) Cloud*, by C.C. Lushbaugh, University of Chicago Toxicity Laboratory, August 18, 1942. Div. 9-380.1-M1
4. OSRD 823. *Toxic Effects of Various Arsine Derivatives*, by J. O. Hutchens, D. W. Hein, Lt. Comdr. A. F. Abt (MC) U.S.N.R., Julee H. Last, R. Merrill, and C. C. Lushbaugh, University of Chicago Toxicity Laboratory, August 24, 1942. Div. 9-313.1-M2
5. OSRD 854. *A New Apparatus for Exposure of Small Animals to Volatile Toxic Agents (Benesh Machine)*, by M. A. Lipton and G. J. Rotariu, University of Chicago Toxicity Laboratory, September 7, 1942. Div. 9-372-M3
6. OSRD 883. *Techniques Employed in Toxicity Determination at the University of Chicago Toxicity Laboratory*, University of Chicago Toxicity Laboratory, September 22, 1942. Div. 9-370-M1
7. OSRD 1980. *A Modification of the "Drui"*, by William Bloom, R. G. Murray, Joseph Savit, and J. F. Thomson, University of Chicago Toxicity Laboratory, October 7, 1943. Div. 9-371-M3
8. OSRD 2047. *Improved Micro-Apparatus for Controlled Toxicity Determinations*, by J. O. Hutchens, M. E. Benesh, Jr., H. G. Glass, R. S. Merrill, and H. W. Gurney, University of Chicago Toxicity Laboratory, November 23, 1943. Div. 9-372-M4
9. OSRD 3112. *Automatic Titrator for the Determination of H, L, and Other Gases in Air*, by John H. Northrop, The Rockefeller Institute for Medical Research, January 13, 1944. Div. 9-413.1-M2
10. OSRD 3386. *Tests of Chloramide-Containing Ointments for Protection and Decontamination of Human Skin against Vesicants*, by J. Savit, J. F. Thomson, E. Goldwasser, P. DeBruyn, and Margaret A. Bloom, University of Chicago Toxicity Laboratory, March 21, 1944. Div. 9-311-M2
11. OSRD 3944. *A Vapor Train Study of the Comparative Vesicancy of Mustard and Several Related Amines and Sulfides on Human Skin*, by Simon Black, K. P. DuBois, and M. A. Lipton, University of Chicago Toxicity Laboratory, August 30, 1944. Div. 9-361.1-M1
12. OSRD 4218. *An Electronic Interval Timer for the Northrop Titrimeter*, by C. Ernst Redemann, University of Chicago Toxicity Laboratory, October 6, 1944. Div. 9-413.1-M4
13. OSRD 4230. *The Benesh Micropipette (with Illustrative Vesicant Data)*, by William Bloom, J. F. Thomson, E. Goldwasser, J. Savit, and P. DeBruyn, University of Chicago Toxicity Laboratory, October 9, 1944. Div. 9-371-M4
14. OSRD 4585. *A New Chamber for the Determination of Toxicities by Total, Body, or Head Exposure*, by J. O. Hutchens, H. W. Gurney, H. S. Merrill, H. G. Glass, H. G. Album, and James H. M. Henderson, University of Chicago Toxicity Laboratory, January 17, 1945. Div. 9-372-M5
15. OSRD 4627. *The Recovery of H Vapor from Air by Bubblers Containing 50% Acetic Acid, Diethyl Phthalate, 0.5N Sulfuric Acid, Ethanol or Pyridine B'*, by Clark Gould and others, January 25, 1945. Div. 9-122.117-M1
16. OSRD 4639. *The Intrapulmonic Accumulation and Effects of Inhaled Lubricating Oil and S.G.F. No. 1 Oil in Mon-*

krys, by C. C. Lushbaugh, C. Ernst Redemann, and J. Savit, University of Chicago Toxicity Laboratory, January 27, 1945. Div. 9-386.1-M2

17. OSRD 4855. *The Penetration of Vesicant Vapors into Human Skin*, by Max Bergmann, J. S. Fruton, Calvin Columbic, Stephen M. Nagy, Mark A. Stahmann, and William H. Stein, The Rockefeller Institute for Medical Research, March 24, 1945. Div. 9-361.1-M2
18. OSRD 5181. *The Penetration of Vesicant Vapors into Human Skin (Supplement to OSRD 4855)*, by Max Bergmann, Joseph S. Fruton, Stephen M. Nagy, and William H. Stein, The Rockefeller Institute for Medical Research, June 6, 1945. Div. 9-361.1-M5
19. OSRD 5525. *Toxicity of Various Preparations of W: A Comparison of Toxicities by Inhalation and by Injection to March 31, 1945* by M. A. Lipton, L. S. Somkin, M. Bernstein, and C. C. Lushbaugh, University of Chicago Toxicity Laboratory, August 31, 1945. Div. 9-341-M2

OSRD INFORMAL REPORTS

21. Contract NDCrc-132, University of Chicago Toxicity Laboratory Informal Monthly Progress Reports on *Toxicity of Chemical Warfare Agents*, NDRC 9:4:1. Div. 9-125-M2
    a. No. 6, July 10, 1943.
    b. No. 7, August 10, 1943.
    c. No. 12, January 10, 1944.
    d. No. 13, February 10, 1944.
    e. No. 14, March 10, 1944.
    f. No. 15, April 10, 1944.
    g. No. 16, June 10, 1944.
    h. No. 18, July 10, 1944.
    i. No. 21, October 10, 1944.
    j. No. 22, November 10, 1944.
    k. No. 24, January 10, 1945.
    l. No. 25, February 28, 1945.

UNITED STATES ARMY REPORTS

Chemical Warfare Service

22. EATR 238. *A Method for the Quantitative Application of Minute Measurable Amounts of Undiluted Liquid Vesicants to the Skin (Rad Method)*, March 24, 1937.
23. EATR 321. *Toxicity Determinations: Fundamentals of Gassing Chamber Operation for Accurate Toxicity Determinations*, May 7, 1940.
24. TDMR 450. *A Capillary Method for Delivering Small Amounts of Vesicant*, October 8, 1942.
25. MD(EA) Report 23. *Apparatus for Determining Retained Dose of Inhaled Toxic Gases*, January 31, 1945.
26. Contract W-49-057-CWS-23, University of Chicago Toxicity Laboratory Rept. No. 56. *The Effects of Temperature, Humidity and Season on the Reactions of Human Skin to Mustard Vapor*, by John C. Troxel and John F. Thomson, November 30, 1945.
27. Contract W-49-057-CWS-23, University of Chicago Toxicity Laboratory Informal Monthly Progress Reports on Toxicity and Irritancy of Chemical Agents.
    a. N.S. No. 1, April 15, 1945.
    b. N.S. No. 2, May 15, 1945.
    c. N.S. No. 3, June 15, 1945.
    d. N.S. No. 4, July 15, 1945.
    e. N.S. No. 5, August 15, 1945.
    f. N.S. No. 7, October 15, 1945.
    g. N.S. No. 8, December 15, 1945.
    h. N.S. No. 9, February 15, 1946.
    i. N.S. No. 10, April 15, 1946.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

28. Porton Report No. 2507. *Drop Trap Methods for the Chemical Sampling of Initial Clouds*, August 20, 1943.
29. Ptn. 1601/2 (8.6117A) (8.8996) (8.8953A). (*1*) *The Chemical Selector*, (*2*) *Addendum* (*3*) *The Particle Size Cut-Off in the Chemical Selector*, June 10, 1942.
30. Ptn. 1704 (T.11405). *The Production of Evenly Distributed Droplet Clouds Across Wind Tunnels*, August 30, 1943.
31. Ptn. 1740 (8.2471). *Report on the Production of Drops of Known Size for Experimental Purposes*, February 20, 1942.
32. V.12556. *The Measurement of Small Quantities of Vesicants*, September 16, 1943.

OPEN LITERATURE

33. Drinker, P. *Alternating Current Precipitators for Sanitary Air Analysis 1. An inexpensive precipitator unit.* J. Indust. Hygiene **14**, p. 364–367 (1932).
34. Jacobs, M. B. *Analytical Chemistry of Industrial Poisons, Hazards and Solvents*, **1**, XVIII plus 661 pp. Interscience Press, New York (1941).
35. Jordonais, L. and Nungester, W. J. *Intratracheal Inoculations in the Rat.* Science, **81**, p. 74 (1935).
36. May, K. R. *The Cascade Impactor*, J. of Sci. Inst. (Brit.) **22**, p. 270–277 (1925).
37. Rehberg, P. B. *A Method of Microtitration.* Biochem. Jour. **19**, p. 270–277 (1925).
38. Schoulander, P. F., Edwards, G. A., and Irving, L. *Improved Microneter Burette*, J. Biol. Chem. **148**, p. 495–500 (1943).
39. Trevan, J. W. 1. *An Apparatus for the Measurement of Small Quantities of Liquid.* Lancet, **202**, p. 780 (1922). 2. *The Microneter Syringe.* Biochem. Jour. **19**, p. 1111–1114 (1925).
40. Watson, H. H. *A System for Obtaining Mine Air Dust Samples.* Bull. of the Institution of Mining and Metallurgy No. 380, pp. 1–33 (1936).

Chapter 17

OSRD FORMAL REPORTS

1. OSRD 4020. *An Experimental Investigation of the Physiological Mechanisms Concerned in the Production of Casualties by Flame Thrower Attack*, by F. C. Henriques, Jr., A. R. Moritz, F. R. Dutra, and J. R. Weisiger, Harvard University, August 15, 1944. Div. 9-386.2-M1

2. OSRD 6182. *An Experimental Investigation of the Physiological Mechanisms Concerned in the Production of Casualties by Flame Thrower Attack*, by A. R. Moritz, F. C. Henriques, Jr., Harvard University, October 23, 1945. Div. 9-386.2-M3

MISCELLANEOUS

3. Contract NDCrc-169, Harvard University, A. R. Moritz and F. C. Henriques, Jr. Unreported studies (carried out in part also under a contract between New York University and the Chemical Warfare Service).
   a. Studies by F. C. Henriques, Jr., and K. Lynch, 1945.
   b. Studies by F. C. Henriques, Jr., and A. R. Moritz, 1945.
   c. Studies by A. R. Moritz and F. C. Henriques, Jr., 1945.
4. *Symposium on the Toxicological Aspects of the Flame Thrower*, Dumbarton Oaks, Washington, D. C., January 20, 1945. Div. 9-386.2-M2
   a. *An Evaluation of the Effectiveness of Protective Clothing Against Heat*, by F. C. Henriques, Jr., K. Lynch, and C. Margnetti.
   b. *An Investigation of Certain Time-Energy Relationships in the Production of Casualties by Exposure to Heat*, by A. R. Moritz, F. C. Henriques, Jr., F. R. Dutra, and J. R. Weisiger.

OPEN LITERATURE

5. Altschule, M. D. and Gilligan, D. R., *The Effects on the Cardiovascular System of Fluids Administered Intravenously in Man. II The Dynamics of the Circulation*, J. Clin. Invest., **17**, 401 (1938).
6. Bélehrádek, J., *Temperature and Living Matter*, Borntraeger, Berlin (1935).
7. Bing, F. C. and Baker, R. W., *The Determination of Hemoglobin in Minute Amounts of Blood by Wu's Method*, J. Biol. Chem., **92**, 589 (1931).
8. Brener, H., *Über die Wärmeleitung des Muskels und Fettes*, Pflügers Arch. f. d. ges. Phys., **204**, 442 (1924).
9. Bull, H. B., *Physical Biochemistry*, John Wiley & Sons, Inc. (1943).
10. Campbell, A. C. P., Alexander, L., and Putnam, T. J., *Vascular Pattern in Various Lesions of Human Central Nervous System: Studies with Benzidine Stain*, Arch. Neurol. and Psychiat., **39**, 1150 (1938).
11. Carslaw, H. S., *Mathematical Theory of Conduction of Heat in Solids*, MacMillan Co. (1921).
12. Cattell, J., Editor, *Biological Symposia, Vol. X Frontiers of Cytochemistry*, Cattell Press (1943).
13. Cheer, S. N., *The Effects of High Temperature on the Heart and Circulation in Intact Animals*, Am. J. Physiol., **84**, 587 (1928).
14. Cyon, E., *Ueber den Einfluss der Temperatur-änderungen auf die centralen Enden der Herznerven*, Pflügers Arch. f. d. ges. Phys., **8**, 340 (1874).
15. Ferris, E. B., Blankenhorn, M. A., Robinson, H. W., and Cullen, G. E., *Heat Stroke: Clinical and Chemical Observations on 44 Cases*, J. Clin. Invest., **17**, 249 (1938)
16. Fick, A., *Ueber Veränderung der Temperatur des im Hirn Cirkulirenden Blutes Einfluss auf die Centra der Herz und Gefässnerven*, Pflügers Arch. f. d. ges. Phys., **5**, 38 (1872).
17. Ford, L. R., *Differential Equations*, McGraw Hill Co. (1933).
18. Gilbert, R. W., *The New High Speed, High Sensitivity Photoelectric Potentiometer*, Rev. Sci. Instrum., **7**, 41 (1936).
19. Glasser, O., Editor, *Medical Physics*, The Year Book Publishers, Inc. (1944).
20. Glasstone, S., Laidler, K. J., and Eyring, H., *The Theory of Rate Processes*, McGraw Hill Co. (1941).
21. Ham, T. H., *Studies of Destruction of Red Blood Cells I Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria: An Investigation of the Mechanism of Hemolysis, with Observations on Five Cases*, Arch. Int. Med., **64**, 1271 (1939).
22. Hardy, J. D. and Soderstrom, G. F. *Heat Loss from the Nude Body and Peripheral Blood Flow at Temperatures of 22 to 35° C.*, J. Nutrition, **16**, 493 (1939).
23. Harris, A. S. and Randall, W. C., *Mechanisms Underlying Electrocardiographic Changes Observed in Anoxia*, Am. J. Physiol., **142**, 452 (1944).
24. Heilbrunn, L. V., *An Outline of General Physiology*, W. B. Saunders Co (1943).
25. Heymans, C., *La tachycardie et la tachypnée pendant l'hyperthermie par le bleu de méthylène*, Arch. Internat. d. Pharmacodyn. et Therap., **28**, 51 (1923).
26. Heymans, C. and Laden, A., *Recherches Physiologiques et Pharmacologiques Sur la Tête Isolée et le Centre Vague Du Chien. I. Anémie, asphyxie, hypertension, adrénaline, tonus pneumogastrique, hyperthermie*, Arch. Internat., de Pharmacodyn. et Therap., **30**, 415 (1925).
27. Kalmi, H. and Levine, M., *Capillary Emboli as a Lethal Factor in Burns*, Science, **48**, 476 (1942).
28. Kahn, R. H., *Ueber die Erwärmung des Carotidenblutes*, Arch. f. Anat. u. Physiol. Leipzig Suppl. Bd., 81 (1904).
29. King, W. J., *The Basic Laws and Data of Heat Transmission. III Free Convection*, Mechanical Engineering, **54**, 347 (1932).
30. Ibid., *IV Forced Convection*, Ibid., **54**, 410 (1932).
31. Knowlton, F. P. and Starling, E. H., *The Influence of Variations in Temperature and Blood Pressure on the Performance of the Isolated Mammalian Heart*, J. Physiol., **44**, 206 (1912).
32. Kramer, B. and Tisdall, F. F., *Distribution of Sodium, Potassium, Calcium and Magnesium Between Corpuscles and Serum of Human Blood*, J. Biol. Chem., **53**, 241 (1922).
33. Lewis, T., *The Blood Vessels of the Human Skin and Their Responses*, Shaw & Sons, London (1927).
34. Lowry, O. H. and Hastings, A.B., *Histochemical Changes Associated with Aging. I. Methods and Calculations*. J. Biol. Chem., **143**, 257 (1942).
35. McAdams, W. H., *Heat Transmission*, McGraw Hill Co. (1942).
36. Moorhouse, V. H. K., *Effect of Increased Temperature of the Carotid Blood*, Am. J. Physiol., **28**, 223 (1911).
37. Moritz, A. R., Henriques, F. C., Jr., and McLean, R., *The Effects of Inhaled Heat on the Air Passages and Lungs*, Am. J. Path., **21**, 311 (1945).

38. Nahum, L. H. and Hoff, H. E., *Observations on Potassium Fibrillation*, J. Pharmacol. and Exp. Therap., **65**, 322 (1939).
39. Pierce, B. O., *A Short Table of Integrals*, Ginn & Co. (1929).
40. Reich, H. V., *Theory and Application of Electron Tubes*, McGraw Hill Co. (1939)
41. Scudder, J., Smith, M. E., and Drew, C. R., *Plasma Potassium Content of Cardiac Blood at Death*, Am. J. Physiol., **126**, 337 (1939).
42. Shen, S. C., Ham, T. H., and Fleming, E. M.: *Studies on Destruction of Red Blood Cells, III. Mechanism and Complications of Hemoglobinuria in Patients with Thermal Burns: Spherocytosis and Increased Osmotic Fragility of Red Blood Cells*. New Eng. J. Med., **229**, 701 (1943).
43. Spaltcholz, W., *Blutgefässe der Haut. Handb. d. Haut. u. Geschlechtskr*, Bd. I. Th., **1**, 379 (1927).
44. Sumner, J. B., and Somers, G. F., *Chemistry and Methods of Enzymes*, Academic Press, Inc. (1943).
45. Uyeno, K., *Studies on the Respiration and Circulation in the Cat III The Effects of Rise of Body Temperature*, J. Physiol., **57**, 203 (1923).
46. White, W. P., *Specific Heats at High Temperatures*, Phys. Rev., **26**, 336 (1908).
47. Wiggers, C. J. and Orias, O., *The Circulatory Changes During Hyperthermia Produced by Short Radio Waves (Radiothermia)*, Am. J. Physiol., **100**, 614 (1932).
48. Winkler, A. W., Hoff, H. E. and Smith, P. K., *Electrocardiographic Changes and Concentration of Potassium in Serum Following Intravenous Injection of Potassium Chloride*, Am. J. Physiol., **124**, 478 (1938).

Chapter 18

OSRD FORMAL REPORTS

1. OSRD 809. *Toxicity and Incidence of Lipid Pneumonia upon Inhalation of Automobile Oil Cloud (SAE No. 10)*, by Clarence C. Lushbaugh and Paul R. Cannon, University of Chicago Toxicity Laboratory, August 18, 1942. Div. 9-326.1-M1
2. OSRD 892. *Toxicity Tests on Salcomine Oxygen and on Salcomine Powder*, by Ellis M. Coon, Howard G. Glass, and Clarence C. Lushbaugh, University of Chicago Toxicity Laboratory, September 22, 1942. Div. 9-314-M1
3. OSRD 3029. *Hypersensitivity and "Flare-Up" Dermatitis Caused by Hexanitrodiphenylamine and Enemy Explosives Containing It*, by John G. Kidd, The Rockefeller Institute for Medical Research, December 23, 1943. Div. 9-321.4-M1
4. OSRD 4630. *The Intrapulmonic Accumulation and Effects of Inhaled Lubricating Oil and of SGF No. 1 Oil in Monkeys*, by Clarence C. Lushbaugh, C. Ernst Reckemann, and Joseph Savit, University of Chicago Toxicity Laboratory, January 27, 1945. Div. 9-326.1-M2

OSRD INFORMAL REPORTS

5. Contract NDCrc-132, University of Chicago Toxicity Laboratory, E. M. K. Geiling, Inf. Month. Prog. Repts. *on Toxicity of Chemical Warfare Agents:*
a. NDRC 9:4:1-17, June 10, 1944, pp. 13-15.
b. NDRC 9:4:1-21, October 10, 1944, pp. 21-25
Div. 9-125-M1
6. Contract OEMsr-260, Arthur D. Little, Inc., *Report on the Effect of Salcomine on Workmen with Summaries of Physical Examination*, February 1, 1944. Div. 11-102.211-M32
7. Contract OEMsr-434, University of Pennsylvania, John A. Goff. *Informal Report on Salcomine Poisoning of Dr. T. A. Geissman*, by Roy W. Benwell, H. A. Stoehr, and T. G. Miller, 1941 Div. 11-102.212-M16

UNITED STATES ARMY REPORTS

Chemical Warfare Service

8. Med. Div. Rept. No. 21. *Medium Lethal Concentrations of H for Mice and Rats for Various Exposure Times*, January 27, 1945.

OPEN LITERATURE

9. Cannon, P. R. *The Problem of Lipid Pneumonia*, J. Am. Med. Assoc., **115**, 2176-2179 (1940).
10. Henderson, Y. and H. W. Haggard, *Noxious Gases*. Second edition. Reinhold Publishing Corp., New York, 1943, pp. 187-192.
11. Landsteiner, K. *Serological and Allergic Reactions with Simple Chemical Compounds*. New England J. Med., **215**, 1189-1204 (1936).
12. Landsteiner, K. and J. Jacobs. *Studies on the Sensitization of Animals with Simple Chemical Compounds II* J. Exp. Med., **64**, 625-639 (1936).
13. Sulzberger, M. B. *Dermatologic Allergy: an Introduction in the Form of a Series of Lectures*. C. C. Thomas, Springfield, Ill., 1940, pp. 23, 33, 37.
14. Twort, C. C. and J. D. Fulton. *Experiments on the Nature of the Carcinogenic Agents in Mineral Oils*. J. Path. Bact., **32**, 149-161 (1929).

Chapter 19

OSRD FORMAL REPORTS

1. OSRD 942. *The β-Chloroethylamines: Kinetics of Displacement, Hydrolysis, and Dimerization of β-Chloroethyldiethylamine, Methyl-bis(β-chloroethyl)amine, and Tris (β-Chloroethylamine) and Their Similarity to the Reactions of HN*, by P. D. Bartlett, Harvard University, October 7, 1942. Div. 9-221.1-M1
2. OSRD 1004. *Reactions of the Chlorine Atoms of Mustard Gas in Aqueous Media*, by W. E. Doering and R. P. Linstead, Harvard University, December 9, 1942. Div. 9-212.11-M4
3. OSRD 1338. *The Preparation of β-Chlorethyl-β'-hydroxyethyl Methylamine and Its Polymerization Products*, by R. L. Shriner, Indiana University, March 15, 1943. Div. 9-221.1-M4
4. OSRD 1430. *Some Reactions of Mustard Gas with Proteins and Proteolytic Enzymes*, by M. Bergmann, J. S. Fruton,

G. W. Irving, S. Moore, and W. H. Stein, The Rockefeller Institute for Medical Research, May 21, 1943. Div. 9-312.12-M2

5. OSRD 1855. *Reactions of the Amine Mustards with Chemical Constituents of Biological Systems*, by J. S. Fruton, M. Bergmann, W. H. Stein, C. Columbie, and M. A. Stahmann, The Rockefeller Institute for Medical Research, September 28, 1943. Div. 9-321.1-M11
6. OSRD 1892. *A Kinetic Study of Ethyl-bis(β-Chloroethyl)-amine (HN-1) in Water-Acetone Solutions and a Comparison with Other β-Chloroethylamines*, by P. D. Bartlett, C. G. Swain, S. D. Ross, and J. W. Davis, Harvard University, October 6, 1943. Div. 9-221.1-M8
7. OSRD 3004. *Selenonium and Sulfonium Halides*, C. D. Hurd, Northwestern University, January 1, 1944. Div. 9-219-M3
8. OSRD 3306. *A Study of the Ability of Compounds with High Competition Factors to Counteract the Injurious Effects of Mustard*, by E. G. Ball, J. M. Buchanan, W. E. Doering, E. E. Maston, R. W. McKee, R. A. Ormsbee, Harvard University, March 16, 1944. Div. 9-322.12-M15
9. OSRD 3437. *A. Investigation of Detoxicants or Decontaminants for Mustard Gas. B. Enzyme Studies and Other Chemical Studies Bearing Upon the Action of Certain Vesicants*, by Leslie Hellerman, Johns Hopkins University, April 4, 1944. Div. 9-322.12-M17
10. OSRD 3557. *Studies on the Kinetics of the β-Chloroethylamines and Their Products in Dilute Aqueous Solution*, by R. Cohen and E. R. Van Artsdalen, Johns Hopkins University, May 1, 1944. Div. 9-221.1-M11
11. OSRD 3620. *The Mechanism of Cutaneous Injury to Mustard Gas. An Experimental Study Using Mustard Prepared with Radioactive Sulfur*, by F. C. Henriques, Jr., A. R. Moritz, H. S. Breyfogle, and L. A. Patterson, Harvard University, May 9, 1944. Div. 9-312.13-M4

11a. OSRD 3660. *The Chemistry of Three Nitrogen Mustards as Water Contaminants*, by A. M. Buswell and C. C. Price, The University of Illinois, May 24, 1944. Div. 9-221.1-M12

12. OSRD 4370. *The Chemistry of Q*, by M. Bergmann, J. S. Fruton, C. Columbie, M. A. Stahmann, and W. H. Stein, The Rockefeller Institute for Medical Research, November 23, 1944. Div. 9-212.113-M2

12a. OSRD 4532. *Synthesis and Characterization of 2-Chloroethyl 2-Hydroxyethyl Sulfide (CH)*, by R. C. Fuson, C. C. Price, H. R. Snyder, E. N. Marvell, and J. B. Ziegler, University of Illinois, January 1, 1945. —— · Div. 9-212.114-M12

13. OSRD 4535. *Chemical Reactions of the Nitrogen Mustards (Supplement to OSRD 1855)*, by M. Bergmann, J. S. Fruton, C. Columbie, M. A. Stahmann, and W. H. Stein, The Rockefeller Institute for Medical Research, January 2, 1945. Div. 9-221.1-M16
14. OSRD 4536. *Chemical Reactions of Semi-H and H*, by M. Bergmann, J. S. Fruton, C. Columbie, M. A. Stahmann, and W. H. Stein, The Rockefeller Institute for Medical Research, January 2, 1945. Div. 9-212.114-M3
15. OSRD 4540. *Chemical Reactions of Divinyl Sulfone, H Sulfone and Divinyl Sulfoxide*, by M. Bergmann, J. S. Fruton, C. Columbie, M. A. Stahmann, and W. H. Stein, The Rockefeller Institute for Medical Research, January 4, 1945. Div. 9-212.3-M1
16. OSRD 4834. *The Chemistry of Sulfonium Salts Related to H*, by M. Bergmann, J. S. Fruton, C. Columbie, M. A. Stahmann, W. H. Stein, The Rockefeller Institute for Medical Research, March 19, 1945. Div. 9-212.3-M2
17. OSRD 4841. *Biochemistry of the Action of the Sulfur-Containing Vesicants*, by V. du Vigneaud, F. H. Carpenter, H. F. McDuffie, Jr., H. McKennis, Jr., D. B. Melville, L. R. Rachele, C. M. Stevens, and L. J. Wood, Cornell University Medical College, March 20, 1945. Div. 9-312.1-M6
18. OSRD 5030. *Some Aspects of the Chemistry of T as a Water Contaminant*, C. C. Price and A. Pohland, University of Illinois, May 2, 1945. Div. 9-212.3-M3
19. OSRD 5202. *Some Aspects of the Behavior of Q as a Water Contaminant*, by C. C. Price and R. M. Roberts, University of Illinois, June 14, 1945. Div. 9-212.113-M3

OSRD INFORMAL REPORTS

20. Contract NDCrc-136, Harvard University, Paul D. Bartlett. Inf. Month. Prog. Rept., October 10, 1943. Div. 9-255-M11
21. Contract OEMsr-80, Harvard University Medical School, Eric G. Ball. Inf. Month. Prog. Rept. (NDRC 9:5:1 No. 7), August 10, 1943. Div. 9-322.12-M4
22. Contract OEMsr-94, Johns Hopkins University, Leslie Hellerman. NDRC B-4C Informal Report No. 2. *Chemical Studies Relating to the Behavior of Certain Vesicants and to the Search for Antidotes*, September 1942. Div. 9-322-M2
23. Contract OEMsr-129, The Rockefeller Institute for Medical Research, John H. Northrop. Inf. Month. Prog. Rept. (NDRC B-4C), April 1942. Div. 9-124-M1
24. Contract OEMsr-313, The Rockefeller Institute for Medical Research, Max Bergmann. Inf. Month. Prog. Rept. (NDRC 9:5:1 No. 3), April 10, 1944. Div. 9-124-M5
25. Contract OEMsr-532, Johns Hopkins University, Barnett Cohen. Inf. Month. Prog. Rept. (NDRC B-4C), April 1943. Div. 9-124-M5
26. Contract OEMsr-563, University of Illinois, Charles C. Price. NDRC 9:3:2 Informal Report No. 65, *The Chemistry of Mustard Gas as a Water Contaminant*, August 21, 1943. Div. 9-212.11-M5
27. Contract OEMemr-51, Yale University, William T. Salter.
    a. *Toxicity of Water Contaminated by TI. 145, TI. 146, TI. 301 and Procedures for Decontamination*, by A. Gilman, L. Goodman, and F. S. Phillips, December 16, 1942. Div. 9-321.1-M3
    b. *Relationship Between Chemical Constitution and Pharmacodynamic Action of the Nitrogen Mustards and Their Transformation Products*, by A. Gilman, L. Goodman, and F. S. Phillips, February 19, 1943. Div. 9-321.1-M6
    c. *Further Studies on the Toxicity of Orally Ingested TI. 145 in Water. The Adequacy of the DB-3 Test for Detection of Toxic Concentrations of TI. 145*, by A. Gilman, L. Goodman, and F. S. Phillips, March 7, 1943. Div. 9-321.1-M7

28. Contract OEMemr-108, University of Pennsylvania, D. Wright Wilson.
   a. *Reaction of Tl. 148 with Hexamethylenetetramine*, by S. Gurin, A. M. Delluva, and D. I. Crandall, April 1, 1943. Div. 9-221.1-M3
   b. *The Reaction of Amines with N-Mustards*, by S. Gurin, D. I. Crandall, and A. M. Delluva, May 14, 1943. Div. 9-221-M1
29. OEMemr-141, Harvard University, D. G. Cogan.
   a. Report No. 9. *A Study of Some of the Reaction Characteristics of Semi-H (β-chloro-β-hydroxyethyl sulfide) and Their Biological Significance*, by V. E. Kinsey and W. M. Grant, January 23, 1943. Div. 9-312.14-M3
   b. Report No. 12. *Preparation of Semi-H*, by V. E. Kinsey and W. M. Grant, May 10, 1943. Div. 9-212.114-M1
   c. Report No. 11. *Studies of Compounds Formed by Reaction with HS or Semi-H and Their Enzymatic Degradation. Part II. Preparation of Semi-H Derivatives of Cysteine and Valine*, by V. E. Kinsey and W. M. Grant, June 16, 1943. Div. 9-312.121-M2

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

30. Porton Memorandum No. 22. *Comprehensive Report on S*, March 5, 1943.
31. Porton Report No. 2247. *The Chemistry of 2,2'-Dichlorethyl Sulfide*, August 1, 1941.
32. Porton Report No 2384. *The Chemistry of S and Related Compounds. Part II. A Preliminary Study of the Action of Water on S*, June 1942.
33. Porton Report No. 2415. *The Chemistry of S and Related Compounds. Part IV. The Synthesis of the Stereoisomeric Forms of S Dimer and S-chlorohydrin Dimer*, September 9, 1942.
34. Porton Report No. 2416. *The Chemistry of S and Related Compounds. Part V. The Preparation of S-chlorohydrin*, September 8, 1942.
35. Porton Report No. 2417. *The Chemistry of S and Related Compounds. Part VI. A Further Study of the Action of Water on S: the Attempted Isolation of the Nematogic Substance SB"*, September 7, 1942.
36. Porton Report No. 2421. *The Toxicity of S in Water*, September 8, 1942.
37. Porton Report No. 2443. *The Dimerization of T.773*, October 27, 1942.
38. Porton Report No. 2454. *The Chemistry of S and Related Compounds. Part VII. Some Reactions of Ethyleniminium S; The Preparation of 3,3'-Dimethyl S*, November 19, 1942.
39. Porton Report No. 2460. *Blood Changes Due to S Derivatives*, December 1, 1942.
40. Porton Report No. 2483. *Chemical Studies on the Mode of Action of Mustard Gas on Proteins. Part I. The Nature of the Combination of H with Proteins*, February 19, 1943.
41. Porton Report No. 2491. *Reactions of Certain Chemical Warfare Agents with Sulfides and Related Compounds*, March 8, 1943.
42. Porton Report No. 2496. *The Action of Water on T.773 (2,2',2"-trichlortriethylamine)*, March 16, 1943.
43. Porton Report No. 2513. *The Chemistry of S and Related Compounds. Part XI. Ethyl-, n-Propyl-, and Isopropyl-bis(β-chloroethyl) Amines*, June 9, 1943.
44. Porton Report No. 2523 (Summary). *The Toxicity by Injection of Nitrogen Vesicants and Their Hydrolysis Products*, July 21, 1943.
45. Porton Report No. 2536. *Chemical Studies on the Mode of Action of Mustard Gas. Part II. The Hydrolysis of the Sulfonium Compounds of H with TG*, August 18, 1943.
46. Porton Report No. 2544. *Chemical Studies on the Mode of Action of Mustard Gas. Part III. The Alkali-Lability of Some Sulfonium Salt Models of 2H-Protein Compounds*, October 26, 1943.
47. Porton Report No. 2587. *The Treatment of Systemic Effects of H. Part I. A Preliminary Survey of Therapeutic Agents of High Competition Factor*, March 10, 1944.
48. Porton Report No. 2658. *The Treatment of Systemic Effects of H. Part II. Dithiocarbamates as Therapeutic Agents*, November 17, 1944.
49. Porton Departmental Report No. 158. *The Chemistry of 2,2'-Dichlorethyl Sulfide*, February 26, 1940.
50. Porton Departmental Report No. 182 and Addendum. *The Chemistry of 2,2'-Dichlorethyl Sulfide. Some Reactions of 2,2'-Dichlorethyl Sulfone and Vinyl Sulfone with Special Reference to Physiological Activity*, May 8, 1940.
51. Ptn. 1217 (R.8051). *The Chemical Aspect of the Sulfone Theory*, March 13, 1941.
52. Ptn. 4310 (T.10053). *The Hydrolysis of H with Small Amounts of Water*, August 7, 1943.

Extramural Research

53. Cambridge Biochemical Laboratory. Wormall Report No. 2 (V.15158A). *Action of H, H-Sulfone, Divinyl Sulfide and Divinyl Sulfone on Amino Acids*, by I. C. Bourneuil, G. E. Francis, and A. Wormall, October 1941.
54. Oxford University, R. A. Peters.
   a. Report No. 1. *The Kinetics of the Replacement of Chlorine in H (Mustard)*, by E. R. Holiday, H. G. Ogston, I. St. I. Philpot, and I. Stocken, not dated.
   b. Report No. 15 (V.13702). *Further Search for Thiol Antidotes for (H) Mustard*, by E. R. Holiday, A. G. Ogston, R. A. Peters, I. St. I. Philpot, and I. A. Stocken, September 24, 1940.
   c. Report No. 34 (V.6838). *On the Characteristics of Reactions in Aqueous Solution Involving the Chlorine Atoms of H. A Recapitulation and Some Further Evidence*, by H. G. Ogston, July 3, 1941.
   d. Report No. 41. (V.15197B). *Preparation and Properties of β-Hydroxyethyl-β-chloroethyl Sulfide*, by A. G. Ogston, November 17, 1941.
   e. Report No. 49 (V.20007). *On the Mechanism of the Physiological Action of Mustard: A Comparison of Some Properties of Mustard and Its Analogs*, by E. R. Holiday and A. G. Ogston, January 1942.
   f. Report No. 53 (W.4154 A). *Identification of Cysteine Among the Products of the Splitting of Thiother Linkages*, by R. H. Peters and R. W. Wakelin, May 1942.

g. Report No. 50 (W.7518). *Further Observations on the Reactions of S in Aqueous Solutions*, by A. G. Ogston, July 8, 1942.

h. Report No. 67. (Y.535B). *On the Relations of CH (H-Chlorhydrin) to Sulfonium Compounds*, by A. G. Ogston, February 24, 1943.

i. U.20573B. *The Present Position of the "Sulfone" Theory*, by R. A. Peters, January 24, 1941.

j. U.22140. *A Summary of Some Features of Work Upon H Since the Last War*, by R. A. Peters and associates, February 4, 1941.

k. W.4154A. *The Splitting of the Thioether Linkage in Certain Derivatives of Mustard*, by A. H. Ford-Moore, R. A. Peters, and R. W. Wakelin, May 11, 1942.

l. Z.8310. *A Note of Prof. Peters on His Investigation on the Attempted Removal of Combined Mustard, Together with Some Comments on the American Work*, July 1944.

CANADIAN REPORTS

Chemical Warfare Laboratories, Ottawa

55. Physiological Section Report No. 38. *The Reaction of H with Glycine Ethyl Ester*, May 5, 1944.

56. Physiological Section Report No. 46. *The Reaction of H with Serum Proteins in the Presence of Phosphate*, November 9, 1944.

Extramural Research

57. Queens University, R. G. Sinclair, *The Preparation of Sulfur-Containing Lipid Compounds by Reaction of Lipids with Mustard*, by R. G. Sinclair and L. Chipman.

58. University of Alberta, R. B. Sandin. *Studies on S*, by R. B. Sandin, March 9, 1943.

OPEN LITERATURE

59. Alexander, J. R. and McCombie, H., *The Reactions of Divinyl Sulfide, Sulfoxide and Sulfone*, J. Chem. Soc., 1931 (1913).

60. Cashmore, A. E. and McCombie, H., *The Interaction of β,β'-Dichlorodiethyl Sulfide, Sulfoxide and Sulfone with Glycine Ester and Potassium Phthalimide*, J. Chem. Soc., 123, 2884 (1923).

61. Clarke, H. T., *β-Alkyl-1,4-thianes*, J. Chem. Soc., 101, 1585 (1912).

62. Clayton, W. R. and Reid, E. E., *Some Esters of Thiodiglycol*, J. Am. Chem. Soc., 64, 1008 (1942).

63. Davies, W. *Synthetical Experiments with β,β'-Dichlorodiethyl Sulfide*, J. Chem. Soc., 117, 297 (1920).

64. Davies, J., and Oxford, J., *Formation of Sulfonium Chlorides and of Unsaturated Substances by the Action of Water and of Aqueous Alcoholic Potash on β,β'-Dichlorodiethyl Sulfide*, J. Chem. Soc., 1931, 224.

65. Ettel, V. and Kohlik, A., *Sur les Composes de β-Hydroxyethylsulfonium*, Coll. Czech. Chem. Comm., 3, 585 (1931).

66. Flury, F., and Wieland, H., *Über Kampfgasvergiftungen VII. Die Pharmakologische Wirkung des Dichlorathylsulfids*, Zeit. ges. Exptl. Med., 12, 307 (1921).

67. Freundlich, H., et al. *Ueber die Kinetik der Umwandlung von Chloralkylaminen in Heterocyklische Verbindungen*, Z. Physik. Chem., 76, 70 (1911); 79, 681 (1912); 101, 177 (1922); 122, 39 (1926); 166A, 161 (1933).

68. Helfrich, O. B., and Reid, E. E., *Reactions and Derivatives of β,β'-Dichlorethyl Sulfide*, J. Am. Chem. Soc., 42, 1208, 1232 (1920).

69. Johnson, J. D. A., *Some Physical Constants of Thiuram, Selenuram and Dithiuram*, J. Chem. Soc., 1933, 1530.

70. Kretov, A. E., *Action of Zinc Dust and Zinc Oxide on Halogen Compounds of Sulfoxides and Sulfones of the Aliphatic Series. Divinyl Sulfone, Vinyl-β-Chlorethyl Sulfone and Their Derivatives*, J. Russ. Phys. Chem. Soc., 62, 1 (1930); C. H. 1930, II, 2309.

71. Lawson, W. E., and Reid, E. E. *Reactions of β,β'-Dichlorethyl Sulfide with Amino Compounds*, J. Am. Chem. Soc., 47, 2821 (1925).

72. Major, R. T., *Un Ether Aminobenzoique du Thiodiglycol et un Sulfone. Nouvel Homologue Superieur du Thiodiglycol*, Bull. Soc. Chim., (4) 41, 634 (1927).

73. Marshall, E. K., Jr., and Williams, T. W., *The Toxicity and Skin Irritant Effect of Certain Derivatives of Dichlorethyl Sulfide*, J. Pharm. Exp. Therap., 16, 239 (1920).

74. Nenitzescu, C. D., and Scarlatescu, N., *Über eine Eigentumliche Umsetzung des β,β'-Dichlor-diathylsulfids mit Halogenverbindungen*, Ber. Chem. Ges., 67, 1142 (1934).

75. Peters, R. A., and Walker, E., *Rate of Liberation of Acid by β,β'-Dichlorodiethyl Sulfide and its Analogues in its Relation to the "Acid" Theory of Skin Vesication*, Biochem. J., 17, 200 (1923).

Chapter 20

OSRD FORMAL REPORTS

1. OSRD 723. *The Hydrolysis of β,β'-Dichlorodiethylsulfide (DH) in the Vapor Phase. The Quantitative Estimation of DH in Solution*, by Charles C. Price, University of Illinois, June 15, 1942. Div. 9-212.112-M2

2. OSRD 942. *The β-Chloroethylamines: Kinetics of Displacement, Hydrolysis, and Dimerization of β-Chloroethyldiethylamine, Methyl-bis-β-chloroethylamine, and tris-β-Chloroethylamine and Their Similarity to the Reactions of HN*, by Paul D. Bartlett, Harvard University, October 7, 1942. Div. 9-221.1-M1

3. OSRD 1094. *Reactions of the Chlorine Atoms of Mustard Gas in Aqueous Media*, by W. E. Doering and R. P. Linstead, Harvard University, December 9, 1942. Div. 9-212.11-M4

4. OSRD 1131. *Summary of the Biochemical and Pharmacological Properties of the Amine Mustards*, by Homer W. Smith, December 9, 1943. Div. 9-321.1-M2

5. OSRD 1438. *The Reactions of DH, TL.101, TL.120 and TL.143 with Some Chemical Constituents of Biological Systems*, by Max Bergmann, William H. Stein, Joseph S. Fruton, Calvin Golumbic, and Mark A. Stahmann, The Rockefeller Institute for Medical Research, May 21, 1943. Div. 9-301.3-M1

6. OSRD 1439. *Some Reactions of Mustard Gas with Proteins and Proteolytic Enzymes*, by Max Bergmann, J. S. Fruton,

G. W. Irving, S. Moore, and W. H. Stein, The Rockefeller Institute for Medical Research, May 21, 1943.
Div. 9-312.12-M2

7. OSRD 1570. *The β-Chloroethylamines: A Further Kinetic Analysis of the Dimerization and Hydrolysis of Methyl-bis-β-chloroethylamine; Further Observations of Diethyl-β-chloroethylamine and tris-β-Chloroethylamine*, by Paul D. Bartlett, Sidney D. Ross, and C. Gardner Swain, Harvard University, July 6, 1943. Div. 9-221.1-M6
8. OSRD 1672. *The Kinetics of Oxidation of β,β'-Dichlorodiethylsulfide and Thiodiglycol*, by Paul D. Bartlett and Sidney D. Ross, Harvard University, August 5, 1943.
Div. 9-512-M4
9. OSRD 1855. *The Reactions of Amine Mustards with Chemical Constituents of Biological Systems*, by Joseph S. Fruton, Max Bergmann, William H. Stein, Calvin Columbie, and Mark A. Stahmann, The Rockefeller Institute for Medical Research, September 28, 1943.
Div. 9-321.1-M11
10. OSRD 1892. *A Kinetic Study of Ethyl-bis-β-chloroethylamine (HN-1) in Water-Acetone Solutions and a Comparison with other β-Chloroethylamines*, by Paul D. Bartlett, C. Gardner Swain, Sidney D. Ross, and James W. Davis, Harvard University, October 6, 1943. Div. 9-221.1-M8
11. OSRD 3557. *Studies on the Kinetics of the β-Chloroethylamines and Their Products in Dilute Aqueous Solution*, by Barnett Cohen, Joseph Harris, and Ervin R. Van Artsdalen, The Johns Hopkins School of Medicine, May 1, 1944. Div. 9-221.1-M11
12. OSRD 3605. *The Reactivity of Chlorine in β,β'-Dichlorodiethyl Ether, 2,4-Dichlorotetrahydrothiophene and bis-1,3-Dichloro-2-propyl Sulfide*, by Paul D. Bartlett and Edward S. Lewis, Harvard University, April 6, 1944.
Div. 9-212.11-M6
13. OSRD 3620. *The Mechanism of Cutaneous Injury by Mustard Gas. An Experimental Study Using Mustard Prepared with Radioactive Sulfur*, by F. C. Henriques, Jr., A. R. Moritz, H. S. Breyfogle, and L. A. Patterson, Harvard University, May 9, 1944. Div. 9-312.13-M4
14. OSRD 3660. *The Chemistry of Three Nitrogen Mustards as Water Contaminants*, by Arthur M. Buswell and Charles C. Price, May 24, 1944 Div. 9-221.1-M12
15. OSRD 4535. *Chemical Reactions of the Nitrogen Mustards* (Supplement to OSRD 1855) by Max Bergmann, Joseph S. Fruton, Calvin Columbie, Mark A. Stahmann, and William H. Stein, The Rockefeller Institute for Medical Research, January 2, 1945. Div. 9-221.1-M16
16. OSRD 4536. *Chemical Reactions of Semi-H and H*, by Max Bergmann, J. S. Fruton, C. Columbie, M. A. Stahmann, and W. H. Stein, The Rockefeller Institute for Medical Research, January 2, 1945. Div. 9-212.114-M3
17. OSRD 4546. *Chemical Reactions of Divinyl Sulfone, H Sulfone and Divinyl Sulfoxide*, by Max Bergmann, Joseph S. Fruton, Calvin Columbie, Mark A. Stahmann, and William H. Stein, The Rockefeller Institute for Medical Research, January 4, 1945. Div. 9-212.3-M1
18. OSRD 4683. *The Mechanism of Hydrolysis and Displacement of Mustard Chlorohydrin and Mustard in Aqueous Solutions*, by Paul D. Bartlett and C. Gardner Swain, Harvard University, February 10, 1945.
Div. 9-212.11-M12
19. OSRD 3030. *Some Aspects of the Chemistry of T as a Water Contaminant*, by Charles C. Price and Albert Poliard, University of Illinois, May 2, 1945. Div. 9-212.3-M3
20. OSRD 5146. *Final Report and Summarization of NDRC Work*, by Barnett Cohen, Joseph Harris, E. R. Van Artsdalen, and Marie E. Perkins, The Johns Hopkins School of Medicine, May 20, 1945. Div. 9-200-M10
21. OSRD 5202. *Some Aspects of the Behavior of Q as a Water Contaminant*, by Charles C. Price and Royston M. Roberts, University of Illinois, June 14, 1945.
Div. 9-212.113-M3

OSRD INFORMAL REPORTS

22. Contract OEMsr-129, The Rockefeller Institute for Medical Research, John H. Northrop. Inf. Month. Prog. Rept. (NDRC 9:5:1 No. 1), February 10, 1943.
Div. 9-124-M1
23. Contract OEMsr-214, Johns Hopkins University, W. Mansfield Clark.
    a. Inf. Month. Prog. Rept. (NDRC B4-C'), April 25, 1942. Div. 9-212.112-M1
    b. Informal Report (NDRC B4-C'), December 1, 1941 to June 1, 1942. Div. 9-212.11-M1
24. Contract OEMsr-313, The Rockefeller Institute for Medical Research, Max Bergmann. Inf. Month. Prog. Repts. Div. 9-124-M5
    a. NDRC 9:5:1 No. 3, April 10, 1943.
    b. NDRC 9:5:1 No. 6, July 10, 1943.
    c. NDRC 9:5:1 No. 11, December 10, 1943.
25. Contract OEMsr-532, Johns Hopkins University, Barnett Cohen. Inf. Month. Prog. Repts. Div. 9-221.1-M9
    a. NDRC 9:5:1 No. 10, November 10, 1943.
    b. NDRC 9:5:1 No. 12, January 10, 1944.
    c. NDRC 9:5:1 No. 13, February 10, 1944.
    d. NDRC 9:5:1 No. 14, March 10, 1944.
    e. NDRC 9:5:1 No. 17, June 10, 1944.
    f. NDRC 9:5:1 No. 20, September 10, 1944.
    g. NDRC 9:5:1 No. 22, November 10, 1944.
    h. NDRC 9:5:1 No. 23, December 10, 1944.
    i. NDRC 9:5:1 No. 24, January 10, 1945.
26. Contract OEMsr-303, University of Illinois, Charles C. Price. NDRC 9:3:2 Informal Report No. 05, *The Chemistry of Mustard Gas as a Water Contaminant*, August 21, 1943. Div. 9-212.11-M5
27. Contract OEMsr-910, Case School of Applied Science, Mathew M. Braidech. Inf. Month. Prog. Repts., February 10 and March 10, 1944. Div. 9-501-M3
28. Contract OEMcmr-108, University of Pennsylvania, D. Wright Wilson. Report on *The Reaction of Amines with Nitrogen Mustards*, by Samuel Gurin, Dana L. Crandall, and Adelaide Delluva, May 14, 1943.
Div. 9-221-M1
29. Contract OEMcmr-141, Harvard University Medical School, David C. Cogan.
    a. Report No. 7. *Direct Determination of the Effect of Temperature and Chloride Ions on the Hydrolysis of HS Distinguished from β-Chloro-β'-hydroxyethyl Sulfide*, by V. E. Kinsey and W. M. Grant, January 14, 1943. Div. 9-212.112-M7

b. Report No. 9. *A Study of Some of the Reaction Characteristics of Semi-H, (β-Chloro-β'-hydroxydiethyl Sulfide) and their Biological Significance*, by V. E. Kinsey and W. M. Grant, January 23, 1943. Div. 9-312.14-M3

c. Report No. 45. *Measurement of Rate of Reaction of H in Blood*, by V. E. Kinsey and W. M. Grant, January 2, 1945. Div. 9-312.14-M7

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

30. Porton Report No. 2384. *The Chemistry of S and Related Compounds. II. A Preliminary Study of the Action of Water on S*, June 1942.

31. Porton Report No. 2422. *The Dimerization of S. Part I*, September 10, 1942.

32. Porton Report No. 2443. *The Dimerization of T.273*, October 27, 1942.

33. Porton Report No. 2495. *The Chemistry of S. Part IX. Kinetics of Dimerization and Alkaline Hydrolysis*, March 15, 1943.

34. Porton Report No. 2496. *The Action of Water on T.273, (2,2',2"-Trichlorotriethylamine)*, March 16, 1943.

35. Porton Report No. 2536. *Chemical Studies on the Mode of Action of Mustard Gas. Part II. The Hydrolysis of Sulfonium Compounds of H with TG*, August 18, 1943.

36. Porton Report No. 4300 (T.5810). *Comparative Rates of Hydrolysis of T.273, S and H*, May 3, 1943.

Research Establishment, Sutton Oak

37. S.O. R 560. *The Kinetics of the Hydrolysis of Vesicants. Part I 2-Chloroethyl-2'-hydroxyethyl Sulfide (ClH)*, January 16, 1942.

38. S.O. R 576. *The Kinetics of the Hydrolysis of Vesicants. Part II. 2,2'-Dichlorodiethyl Sulfide (H)*, March 3, 1942.

39. S.O. R 594. *The Kinetics of the Hydrolysis of Vesicants. Part III. 2,2'-Di(β-chloroethylthio)-diethyl Ether (T.274)*, April 13, 1942.

40. S.O. R 615. *The Rate of Dissolution of 2,2'-Dichlorodiethyl Sulfide (H) in Distilled and Natural Waters*, August 25, 1942.

Extramural Research

41. Oxford Biochemical Laboratory (R. A. Peters)

a. Report No. 1. *The Kinetics of the Replacement of Chlorine in H*, by E. R. Holiday, A. G. Ogston, J. St. L. Philpot, and L. Stocken, undated.

b. Rept. No. 34 (V.4938). *On the Characteristics of Reactions in Aqueous Solution Involving the Chlorine Atoms of H. A Recapitulation and some Further Evidence*, by A. G. Ogston, July 14, 1941.

c. Rept. No. 40 (V.15197A). *Preparation and Properties of β-Hydroxyethyl β'-Chloroethyl Sulfide (H Chlorohydrin, H Half-hydrolysis Product, ClH)*, by A. G. Ogston, November 17, 1941.

d. Rept. No. 49 (V.20007). *On the Mechanism of the Physiological Action of Mustard: A Comparison of some Properties of Mustard and its Analogs*, by E. R. Holiday and A. G. Ogston, January 1942.

e. Rept. No. 54 (W.610). *The Reactions of T.102½ ("S") in Aqueous Solution. Velocity Constants of Hydrolysis of S and H*, by A. G. Ogston, April 4, 1942.

f. Rept. No. 56 (W.7518). *Further Observations on the Reactions of S in Aqueous Solutions*, by A. G. Ogston, July 8, 1942.

g. (Z.14440) (WA-3394-4). *The Reaction Between H and Sodium Monothiophosphate. Some Further Evidence and a New Interpretation*, A. G. Ogston and E. W. Powell, November 1944.

MISCELLANEOUS

42. V.3850. *Notes on an ad hoc Meeting to Discuss Hydrolysis of Vesicants*, Chemical Board, Chemical Subcommittee, March 16, 1943.

CANADIAN REPORTS

Extramural Research

43. Project C.E. 114, McGill University.

a. *The Chemistry of S and Related Compounds. Part II. The Hydrolysis of S Dimers*, by C. A. Winkler, A. L. T. Thompson, and T. J. Hardwick, November 15, 1942.

b. *The Chemistry of S and Related Compounds. Part IV. The Hydrolysis of SH⁺ in Various Acid Solutions*, by C. A. Winkler, A. L. Thompson, and T. J. Hardwick, February 11, 1943.

c. *The Chemistry of S and Related Compounds. Part V. The Reactions of S in Acetone-Water Mixtures*, by C. A. Winkler, A. L. Thompson, and T. J. Hardwick, March 15, 1943.

44. Project C.E. 44, University of Toronto.
The Interaction of Mustard Gas and Blood, by J. A. McCarter, August 1945.

OPEN LITERATURE

45. Cowan, J. C., and Marvel, C. S. *Salts of Polymeric Tertiary Amines*, J. Am. Chem. Soc., **58**, 2277 (1936).

46. Freundlich, H., et al. *Ueber die Kinetik der Umwandlung von Chloralkylaminen in heterocyklische Verbindungen*, Z. physik. Chem., **73**, 79 (1911); **79**, 681 (1912); **101**, 177 (1922); **122**, 39 (1926); **166A**, 161 (1933).

47. Freundlich, H., and Juliusberger, F. *Die Umwandlung von Bromäthylamin in Dimethylenimin-bromhydrat, und ihre Gegenreaktion an Kohle*, Z. physik. Chem., **146**, 321 (1930).

48. Freundlich, H., and Neumann, W. *Ueber die Kinetik der Umwandlung von Halogenalkylaminen in heterocyklische Verbindungen, III.* Z. physik. Chem., **87**, 60 (1914).

49. Freundlich, H., and Salomon, G. *Ueber die Erhöhung der Lebensdauer des β-Phenyl-β-chloräthylamins an Kohle*. Z. physik. Chem., **166A**, 179 (1933).

50. Freundlich, H., and Salomon, G. *Weitere Versuche über die Erhöhung der Lebensdauer von β-Phenyl-β-chloräthylamins an Kohle*. Helv. Chim. Acta, **17**, 88 (1934).

51. Hopkins, F. F. *Solubility and Hydrolysis of Dichlorethylsulfide, with a New Method for Estimating Small Amounts of Same*. J. Pharmacol., **12**, 393 (1919).

52. Lehmann, M. R., Thompson, C. D., and Marvel, C. S. *Quaternary Ammonium Salts from Halogenated Alkyl Dimethylamines. III. Omega-bromoheptyl-, octyl-, nonyl-, and decylidimethylamines*, J. Am. Chem. Soc., **66**, 1977 (1933).
53. Mohler, H., and Hartnagel, J. *Hydrolyse von β,β'-Dichlordiäthylsulfid*, Helv. Chim. Acta, **24**, 384 (1941).
54. Peters, R. A., Walker, E. *Rate of Liberation of Acid by β,β'-Dichlorethyl Sulfide and its Analogues in its Relation to the "Acid" Theory of Skin Vesication*, Biochem. J., **17**, 260 (1923).
55. Salomon, G. *Kinetics of Ring-Formation and Polymerization in Solution*, Trans. Farad. Soc., **32**, 153 (1936); cf. Helv. Chim. Acta, **16**, 1361 (1933).
56. Wilson, R. E., Fuller, E. W., and Schur, M. O. *The Acceleration of the Hydrolysis of Mustard Gas by Alkaline Colloidal Solutions*. J. Am. Chem. Soc., **44**, 2762 (1922).
57. Winstein, S., and Lucas, H. J. *Retention of Configuration in the Reaction of the 3-Bromo-2-butanols with Hydrogen Bromide*. J. Am. Chem. Soc., **61**, 1576, 1581, 2845 (1939).

Chapter 21

OSRD FORMAL REPORTS

1. OSRD 1131. *Summary of the Biochemical and Pharmacological Properties of the Amine Mustards*, by Homer W. Smith, New York University, December 9, 1942. Div. 9-321.1-M2
2. OSRD 1248. *The Inactivation of Enzymes by Mustard Gas*, by R. Keith Cannan, New York University, March 10, 1943. Div. 9-312.12-M1
3. OSRD 1439. *Some Reactions of Mustard Gas with Proteins and Proteolytic Enzymes*, by Max Bergmann, J. S. Fruton, G. W. Irving, S. Moore, and W. H. Stein, The Rockefeller Institute for Medical Research, May 21, 1943. Div. 9-312.12-M2
4. OSRD 1630. *A Study of the Reaction between Mustard Gas and Proteins*, by Selby R. Davis, William F. Ross, and Eric G. Ball, Harvard University, July 22, 1943. Div. 9-312.12-M3
5. OSRD 1717. *Review of the Literature on the Systemic Action of Mustard Gas to August 1, 1943*, by Homer W. Smith, New York University, August 16, 1943. Div. 9-312.14-M5
6. OSRD 1824. *The Action of Mustard Gas on Certain Enzymatic Reactions*, by Ralph W. McKee, Ellen L. Marston, Richard A. Ormsbee, and Eric G. Ball, Harvard University, September 21, 1943. Div. 9-312.12-M4
7. OSRD 1855. *The Reactions of Amine Mustards with Chemical Constituents of Biological Systems*, by Joseph S. Fruton, Max Bergmann, William H. Stein, Calvin Columbic, and Mark A. Stahmann, The Rockefeller Institute for Medical Research, September 28, 1943. Div. 9-321.1-M11
8. OSRD 3137. *A. Investigations of Detoxicants or Decontaminants for Mustard Gas. B. Enzyme Studies and other Chemical Studies Bearing on the Action of Certain Vesicants*, by Leslie Hellerman, Curt C. Porter, J. Logan Irvin, C. A. Presta, and Ann Lindsay, Johns Hopkins University, April 4, 1944. Div. 9-522.12-M17
9. OSRD 3620. *The Mechanism of Cutaneous Injury by Mustard Gas. An Experimental Study Using Mustard Prepared with Radioactive Sulfur*, by F. C. Henriques, Jr., A. R. Moritz, H. S. Breyfogle, and L. A. Patterson, Harvard University, May 9, 1944. Div. 9-312.13-M4
10. OSRD 3653. *Reactions of H with Enzymes and Proteins*, by Roger M. Herriott, M. L. Anson, and John H. Northrop, The Rockefeller Institute for Medical Research, May 20, 1944. Div. 9-312.12-M6
11. OSRD 4272. *The Toxic Action of Mustard on Nitella*, by W. J. V. Osterhout, The Rockefeller Institute for Medical Research, October 23, 1944. Div. 9-312.1-M5
12. OSRD 4841. *Biochemistry of the Action of Sulfur Containing Vesicants*, by Vincent du Vigneaud, F. H. Carpenter, H. F. McDuffie, Jr., H. McKennis, Jr., O. R. Melville, J. R. Rachele, C. M. Stevens, and L. J. Wood, Cornell University, March 20, 1945. Div. 9-312.1-M6
13. OSRD 5245. *Effects of bis(β-chloroethyl) sulfide (H) and bis(β-chloroethyl) methylamine (HN2) on enzymes in vitro and in vivo*, by Carl F. Cori, Sidney P. Colowick, Louis Berger, and Milton W. Stein, Washington University (St. Louis), June 20, 1945. Div. 9-361.3-M3
14. OSRD 6004. *The Effects of Vesicants on Cell Division in Arbacia Punctulata*, by R. K. Cannan and Milton Levy, New York University, June 1, 1946. Div. 9-361.4-M1
15. OSRD 6005. *The Swelling of Cells and Its Inhibition by Vesicants*, by A. E. Benaglia, R. K. Cannan, Mary E. Dumm, and Milton Levy, New York University, June 1, 1946. Div. 9-361.4-M2

OSRD INFORMAL REPORTS

16. Contract OEMsr-123, Washington University (St. Louis), Carl F. Cori. Inf. Month. Prog. Rept., NDRC 9:5:1 No. 15, April 10, 1944. Div. 9-387-M1
17. Contract OEMsr-120, The Rockefeller Institute for Medical Research, John H. Northrop. Inf. Month. Prog. Repts.
    a. Rept. (NDRC B4-C) of May 23, 1942. Div. 9-124-M2
    b. Rept. (NDRC B4-C) of September 19, 1942. Div. 9-124-M4
18. Contract OEMsr-556, New York University, Homer W. Smith. Inf. Month. Prog. Rept., NDRC 9:5:1 No. 9, September 10, 1943. Div. 9-300-M1
19. Contract OEMsr-24, Johns Hopkins University, Alan C. Woods and James S. Friedenwald.
    a. *Preliminary Report of the Injury to the Rabbit's Cornea by Intra-corneal Injection of Various Chemical Agents*, March 13, 1942. Div. 9-384-M1
    b. Report No. 13. *The Effect of HS Vapor on Certain Metabolic Processes in the Excised Beef Cornea*, by Heinz Herrmann, July 2, 1942. Div. 9-312.131-M1
    c. Report No. 16. *The Significance of the Lactic Acid Content of Surviving and HS-Treated Corneas*, by Heinz Herrmann, July 22, 1942. Div. 9-312.131-M2
    d. Report No. 21. *The Inhibiting Action of H.M on Choline Esterase*, by Heinz Herrmann and Fay H. Hickman, November 20, 1942. Div. 9-321.2-M2

e. Report No. 32. *Further Studies on the Effect on the Metabolism of the Cornea Resting from Exposure to HS*, by Heinz Herrmann and Fay H. Hickman, March 27, 1943. Div. 9-312.131-M8

f. Report No. 33. *The Loosening of the Corneal Epithelium by Mustard and Other Agents*, by Heinz Herrmann and Fay Hickman, March 10, 1943. Div. 9-312.131-M9

g. Report No. 37. *The Effect of 1130 on the Mitotic Activity of Corneal Epithelium*, by Jonas S. Friedenwald and Roy O. Scholz, May 31, 1943. Div. 9-321.2-M3

h. Report No. 39. *The Loosening of the Corneal Epithelium by Mustard. II. Effect of Temperature*, by Heinz Herrmann and Fay H. Hickman, September 10, 1943. Div. 9-312.131-M10

i. Report No. 41. *The Effect of H on the Utilization of Ribose and Other Pentoses by the Beef Cornea*, by Heinz Herrmann and Fay H. Hickman, October 1943. Div. 9-312.131-M11

j. Report No. 45. *The Loosening of the Corneal Epithelium. III. Further Studies and an Analysis of Previously Reported Findings*, by Heinz Herrmann and Fay H. Hickman, November 30, 1943. Div. 9-312.131-M12

k. Report No. 46. *Inhibition of Mitosis in Corneal Epithelium. Comparison of the Effects of Mustard, Nitrogen Mustards, I., KB16 and Certain Derivatives of 1130*, by J. S. Friedenwald and Roy O. Scholz, December 15, 1943. Div. 9-384-M3

l. Report No. 50. *Pyruvate Metabolism in Beef Cornea, Normally and after Exposure to H*, by Heinz Herrmann and Fay H. Hickman, April 15, 1944. Div. 9-312.131-M13

m. Report No. 51. *Summary of Current Studies on the Effects of H on Corneal Metabolism*, by Heinz Herrmann, Fay H. Hickman, and Sylvia G. Moses, April 16, 1944. Div. 9-312.131-M14

n. Report No. 54. *The Effect of Various Agents on the Adherence of the Corneal Epithelium*, by Heinz Herrmann, June 10, 1944. Div. 9-384-M4

o. Report No. 55. *The Water Content of the Corneal Epithelium after Treatment with H and other Agents which Loosen the Epithelium*, by Heinz Herrmann, June 17, 1944. Div. 9-312.131-M15

p. Report No. 56. *The Effect of H on the Non-protein Nitrogen of the Cornea*, by Heinz Herrmann and Sylvia G. Moses, July 8, 1944. Div. 9-312.131-M16

q. Report No. 57. *The Utilization of Ammonia by the Cornea after Exposure to H*, by Heinz Herrmann and Sylvia G. Moses, July 10, 1944. Div. 9-312.131-M17

r. Report No. 61. *The Effect of H on the Alkaline Glycerophosphatase of the Corneal Epithelium*, by J. S. Friedenwald and Wilhelm Buschke, August 19, 1944. Div. 9-312.131-M18

s. Report No. 62. *The Healing of Wounds in Corneal Epithelium after Exposure to H*, by J. S. Friedenwald and Wilhelm Buschke, August 22, 1944. Div. 9-312.131-M19

t. Report No. 64. *Possible Products of the Utilization of Pyruvate in the Beef Cornea and the Effect of H on the Utilization of Acetoin and Butyrate by the Tissues*, by Heinz Herrmann and Fay H. Hickman, February 20, 1945. Div. 9-312.131-M20

u. Report No. 66. *Experiments on the Increased Non-protein Nitrogen Level in the Excised Cornea after Exposure to H*, by Heinz Herrmann and Sylvia G. Moses, March 12, 1945. Div. 9-312.131-M21

v. Report No. 67. *Nuclear Fragmentation produced by Mustard and Nitrogen Mustard in the Corneal Epithelium*, by Jonas S. Friedenwald and Wilhelm Buschke, July 10, 1945. Div. 9-321.2-M2

w. Report No. 68. *The Effect of Anaerobiosis upon the Development of Certain Pathological Changes in the Excised Surviving Cornea after Application of H and Various Other Substances*, by Heinz Herrmann and Sylvia G. Moses, July 14, 1945. Div. 9-312.131-M22

x. Report No. 69. *The Effect of Mustard Treatment on the Histological Staining Characteristics of Corneal Tissue*, by Jonas S. Friedenwald and Roy O. Scholz, August 1, 1945. Div. 9-312.131-M23

20. OEMcmr-141, Howe Laboratory of Ophthalmology, Harvard University Medical School, David G. Cogan.

a. Report No. 1. *The Effect of Vesicant Agents under Various Conditions on the Permeability of the Cornea, Conjunctiva and Sclera*, by D. G. Cogan, V. E. Kinsey, and W. M. Grant, July 29, 1942. Div. 9-312.131-M3

b. Report No. 5. *Inhibition of Corneal Swelling Ability by DH in Organic Solvents*, by D. G. Cogan, V. E. Kinsey, and W. M. Grant, October 1, 1942. Div. 9-312.131-M4

c. Report No. 6. *Effects of HS on the Cornea. Conclusions of the Committee on the Treatment of Gas Casualties*, by D. G. Cogan, V. E. Kinsey, and W. M. Grant, December 8, 1942. Div. 9-312.131-M5

d. Report No. 8. *Correlation of Rate of Reaction of HS and HS Intermediates with Corneal Tissue (in vitro) with the Effect Produced*, by V. E. Kinsey and W. M. Grant, December 24, 1942. Div. 9-312.131-M6

e. Report No. 9. *A Study of Some of the Reaction Characteristics of Semi H (β-chloro β'-hydroxy diethylsulfide) and Their Biological Significance*, by W. M. Grant and V. E. Kinsey, January 23, 1943. Div. 9-312.14-M3

f. Report No. 13. *Studies of Compounds Formed by the Reaction with HS or Semi H and Their Enzymatic Degradation. I. The Effect of Gastro-intestinal Enzymes on HS-Cystein as Indicated by Growth Studies Made on Rats and Chicks*, by V. E. Kinsey and W. M. Grant, June 16, 1943. Div. 9-312.121-M1

g. Report No. 14, *Studies of Compounds Formed by Reaction with HS or Semi H and Their Enzymatic Degradation. II. Preparation of Semi H Derivatives of Cystein and Valine*, W. M. Grant and V. E. Kinsey, June 16, 1943. Div. 9-312.121-M2

h. Report No. 15. *Studies of Compounds Formed by Reaction with HS or Semi H and Their Enzymatic Degradation. III. Determination of the Amino Acids made Unavailable for Growth of Rats, by HS Treat-*

ment of Casein. IV. Inability of the Rat to Utilize Valine and Cysteine from Semi-H-valine and Semi-H-cysteine Respectively, by D. G. Cogan, V. E. Kinsey, and W. M. Grant, July 20, 1943. Div. 9-312.121-M3

i. Report No. 18. *Studies of Compounds Formed by Reaction with HS or Semi-H and Their Enzymatic Degradation. V. Determination of the Essential Amino Acids Unavailable for Growth of Rats in an Acid Hydrolysate of Casein Reacted with HS in Alkaline Solution*, by W. M. Grant and V. E. Kinsey, November 20, 1943. Div. 9-312.121-M4

j. Report No. 19. *Studies of Compounds Formed by Reaction with HS or Semi H and Their Enzymatic Degradation. VI. Determination of Essential Amino Acids of Casein Rendered Unavailable for the Growth of Rats by Reaction of Casein with HS in Neutral Solutions*, by W. M. Grant and V. E. Kinsey, November 20, 1943. Div. 9-312.121-M5

k. Report No. 20. *Studies of Compounds Formed by Reaction with HS or Semi H and Their Enzymatic Degradation. VII. Preliminary Report on the Use of Enzymes from Soil Bacteria to Degrade Mustard Derivatives*, by V. E. Kinsey and W. M Grant, November 20, 1943. Div. 9-312.121-M6

l. Report No. 21. *Some Observations of the Effects of H on the Yeast Cell*, by V. E. Kinsey and W. M. Grant, December 1943. Div. 9-312.11-M2

m. Report No. 22. *Studies of Compounds Formed by Reaction with HS or Semi H and Their Enzymatic Degradation VIII. Semi-quantitative Determination of Amino Acids Affected by Reaction of H with Proteins as Determined by Bacteriological Assay*, by V. E. Kinsey and W. M. Grant, December 1, 1943. Div. 9-312.12-M5

n. Report No. 22 (note conflict with above). *A Comparison of the Effects Produced in Yeast Cells by Different Toxic Agents with Reference to their Mode of Action and Lability of Reaction Products Formed*, by V. E. Kinsey and W. M. Grant, January 7, 1944. Div. 9-382-M1

o. Report No. 23. *Correlation of Inhibition of Cell Division with Binding of Intra-cellular Glutathione by Yeast*, by W. M. Grant and V. E. Kinsey, January 10, 1944. Div. 9-312.11-M3

p. Report No. 24. *Some Factors Affecting the Toxicity of Divinylsulfone for Yeast and Reversal of the Toxic Effect by Various Means*, by V. E. Kinsey and W. M. Grant, February 24, 1944. Div. 9-312.3-M2

q. Report No. 25. *Reactions of Divinylsulfone Considered in Relation to Reversal of its Effect on the Cell*, by W. M. Grant and V. E. Kinsey, March 6, 1944. Div. 9-312.3-M3

r Report No. 26. *Reaction of Divinylsulfone with Glutathione in Yeast and Relation between Effect and Diminution of Glutathione*, by V. E. Kinsey and W. M. Grant, March 7, 1944. Div. 9-312.3-M4

s. Report No. 27. *Use of Peracids in Yeast in an Attempt to Oxidize the Sulfur of Fixed H to the Sulfone*, by V. E Kinsey and W. M. Grant, March 9, 1944. Div. 9-312.11-M4

t. Report No. 28. *Study of Dissociation of Bound H Produced by Oxidative Conditions Compatible with Cell Life*, by W. M. Grant and V. E. Kinsey, April 5, 1944. Div. 9-322.12-M18

u. Report No. 30. *Further Studies on the Relation between Inhibition of Rate of Cell Division and Concentration of H and Divinylsulfone*, by V. E. Kinsey and Helen Penta, May 11, 1944. Div. 9-312.111-M1

v. Report No. 31. *Injurious Effects of H and Divinylsulfone on Metabolism of Yeast Cells and Results of Several Methods of Therapy*, by V. E. Kinsey and W. M. Grant, May 11, 1944. Div. 9-312.111-M2

w. Report No. 33. *The Relation between the Effects Produced by H and Divinylsulfone on the Rate of Cell Division and Metabolism of Growing Yeast Cells*, by V. E. Kinsey and Phyllis Robison, May 17, 1944. Div. 9-312.111-M3

x. Report No. 34. *A Study of the Reactivity of Yeast DPN, ATP, Adenylic Acid, and Nicotinic Acid with H*, by V. E. Kinsey and W. M. Grant, May 23, 1944. Div. 9-312.11-M5

y. Report No. 37. *A Study of the Reactivity of Yeast with Several Concentrations of H*, by V E. Kinsey, W. M. Grant, F. Henriques, and L. A. Patterson, August 18, 1944. Div. 9-312.11-M6

z. Report No. 38. *A Study of the Reactivity of Yeast with Several Concentrations of H in the Presence and Absence of NaCl*, by V. E. Kinsey, W. M. Grant, F. Henriques, and L. A. Patterson, August 18, 1944. Div. 9-312.11-M7

aa. Report No. 39. *An Investigation of the Distribution of Fixed H in Yeast*, by W. M. Grant, V. E. Kinsey, F. Henriques, and L. A. Patterson, August 18, 1944. Div. 9-312.11-M8

bb. Report No. 41. *Determination of the Effect of Detoxifying Treatment on the Persistence of Divinylsulfone in Yeast Cells*, by W. M. Grant, V. E. Kinsey, F. C. Henriques, and L. A. Patterson, October 30, 1944. Div. 9-312.3-M5

cc. Report No. 42. *Some Biological Aspects of the Reaction of H with Yeast Cells*, by V. E. Kinsey and W. M. Grant, December 28, 1944. Div. 9-312.11-M9

dd. Report No. 43. *The Effect of H on Synthesis of Carbohydrate by Yeast*, by V. E. Kinsey and W. M. Grant, December 28, 1945. Div. 9-312.11-M10

ee. Report No. 44. *Observations on the Permeability of Normal and H-Exposed Yeast Cells*, by W. M. Grant and V. E. Kinsey, December 28, 1944. Div. 9-312.11-M11

ff. Report No. 45. *Measurement of Rate of Reaction of H in Blood*, by W. M. Grant and V. E. Kinsey, January 2, 1945. Div. 9-312.14-M7

gg. Report No. 46. *Further Investigation of Irreversible H Poisoning in Yeast*, by W. M. Grant and V. E. Kinsey, February 8, 1945. Div. 9-312.11-M12

hh. Report No. 47. *Comparison of Toxicity of HN2 amine and HN2 Imine and Toxicity of HN3 to Yeast*, by V. E. Kinsey and W. M. Grant, March 16, 1945. Div. 9-321.1-M16

ii. Report No. 48. *Characteristics of Sulfhydryl-dependent Enzyme Poisoning by H. I. Factors Influencing the Inactivation of Urease by DH, Semi H, DVS, Divinylsulfoxide and Silver Nitrate*, by W. M. Grant and V. E. Kinsey, March 26, 1945. Div. 9-312.12-M7

jj. Report No. 49. *The Lethal Effect of Various Doses of H and Divinyl sulfone on Yeast Cells*, by V. E. Kinsey and W. M. Grant, May 14, 1945. Div. 9-312.111-M4

kk. Report No. 50. *Characteristics of Sulfhydryl Dependent Enzyme Poisoning by H. II. Additional Factors Influencing the Inactivation of Urease by DH, Divinylsulfone and Silver Nitrate*, by W. M. Grant and V. E. Kinsey, May 28, 1945. Div. 9-312.12-M8

ll. Report No. 51. *Characteristics of Sulfhydryl Dependent Enzyme Poisoning by H. III. Toxicity of the Conditions of Silver Treatment Effective in Regeneration of Cysteine from Combination with DVS*, by W. M. Grant and V. E. Kinsey, June 1, 1945. Div. 9-312.12-M9

mm. Report No. 52. *Characteristics of Sulfhydryl Dependent Enzyme Poisoning by H. IV. Protection of Urease during Ag Treatment*, by W. M. Grant and V. E. Kinsey, July 22, 1945. Div. 9-312.12-M10

nn. Report No. 53. *Further Studies on the Mechanism of Poisoning of Yeast by Divinylsulfone*, by V. E. Kinsey and W. M. Grant, August 9, 1945. Div. 9-312.3-M6

21. Contract OEMcmr-57, University of Chicago, E. S. Guzman Barron.

a. Preliminary Report on *The Effect of 1070 and 1130 on the Metabolism of Tissue Slices and Some Enzyme Systems*, by E. S. Guzman Barron, Zelma Baker Miller, Grant Bartlett, and J. Meyer, September 18, 1942. Div. 9-321.2-M1

b. *The Effect of TL145 (tris(β-chloroethyl) amine) and TL146 (bis(β-chloroethyl) methylamine) on the Metabolism of Tissues and on the Activity of Some Enzyme Systems*, by E. S. Guzman Barron, Zelma Baker Miller, Grant Bartlett, and Joseph Meyer, December 18, 1942. Div. 9-321.1-M4

c. *The Metabolism of Lung Tissue as Determined by a Study of Slices and Surround Tissue*, by E. S. Guzman Barron, Zelma Baker Miller, and Grant Bartlett, March 8, 1943. Div. 9-386-M1

d. *Tissue Metabolism and the Activity of Some Enzyme Systems in Rats Gassed with TL146 (HN2)*, by E. S. Guzman Barron, Zelma Baker Miller, Grant Bartlett, and Joseph Meyer, May 26, 1943. Div. 9-321.1-M10

e. *Effect of BAL on Respiration and Glycolysis of H Treated Rat Skin*, by E. S. Guzman Barron and Joseph Meyer, January 21, 1944. Div. 9-522.11-M3

f. *Tissue Metabolism, Glycogen Synthesis of the Liver and Intestinal Absorption of Glucose on H Treated Rats*, by E. S. Guzman Barron and Ulric A. Presta, July 2, 1945. Div. 9-312.14-M8

UNITED STATES ARMY REPORTS

22. EAMRD 24. *The Chemical Action of Mustard within the Body*, October 10, 1924.

UNITED STATES PUBLIC HEALTH SERVICE REPORTS

23. *Toxic Action of β,β'-dichlorethyl Sulfide (Mustard Gas)*, by Carl Voegtlin, et al., National Cancer Institute, National Institute of Health, undated (received by NDRC on August 30, 1943).

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

24. Porton Report No. 158. *The Chemistry of 2,2'Dichlorethyl Sulphide*, February 14, 1940.

25. Porton Report No. 182. *The Chemistry of 2,2' Dichlorethyl Sulphone and Vinyl Sulphone with Special Reference to Physiological Activity*, April 23, 1940, and *Addendum*, September 16, 1940.

26. Porton Report No. 1217. *The Chemical Aspects of the "Sulphone" Theory*, March 13, 1941.

27. Porton Report No. 1217. *Energetics of the Conversion of Mustard to Mustard Sulphone*, July 11, 1941.

28. Porton Report No. 2247. *The Chemistry of H with Special Reference to Its Physiological Action*, July 7, 1941.

29. Porton Report No. 2411. *Some Effects of S-hydrochloride Solution on Cells and Tissues in Vitro*, August 29, 1942.

30. Porton Report No. 2466. *Blood Changes Due to S. Derivatives*, December 1, 1942.

31. Porton Report No. 2526. *The Solubility in vitro of Serum and Bone Marrow, from H Poisoned Animals*, August 14, 1943.

32. Porton Report No. 2543. *Capillary Permeability Factors Related to the Action of C.W. Agents. Part I. Demonstration of the Presence of Such Factors in Certain C.W. Pathological Exudates*, September 21, 1943.

33. Porton Report No. 2590. *Bone Marrow Cultures as Test Objects for the Treatment of Injury due to C.W. Agents*, January 29, 1944.

34. Porton Report No. 2800. *The Biochemical Mode of Action of Mustard Gas. A Review*, October 2, 1943.

35. Porton Report No. 2820. *Comparison of the Effect of H and of Lewisite on Living Tissues*, July 10, 1943.

Extramural Research

36. Oxford Biochemical Laboratory (R. A. Peters)

a. Report No. 1 (U.6437). *The Kinetics of the Replacement of Chlorine in H*, by E. R. Holiday, A. G. Ogston, J. St. L. Philpot, and L. Stocken, undated.

b. Report No. 2. *The Relation Between Toxicity to the Pyruvate Oxidase System and Vesicant Action*, by R. A. Peters and R. W. Wakelin.

c. Report No. 7 (U.3284). *Further Study of Possible Antidotes to H (Mustard)*, by E. R. Holiday, A. G. Ogston, J. St. L. Philpot, and L. Stocken, May 4, 1940.

d. Report No. 15 (U.13762). *Further Search for Thiol Antidotes to H (Mustard)*, by E. R. Holiday, A. G. Ogston, R. A. Peters, J. St. L. Philpot, and L. Stocken, September 21, 1940.

e. Report No. 21 (W.257). *Provisional Note on T1024*, by E. R. Holiday, A. G. Ogston, L. Stocken, R. H. S. Thompson, and Whittaker, March 27, 1942.

f. Report No. 28 (V.20065). *Effect of Substances Other than H upon Some Dehydrogenases*, by R. A. Peters and R. W. Wakelin, January 24, 1941.

g. Report No. 30 (V.14978). *Observations upon the Nature of the Compounds of Mustard Gas and Keratin. Part I. Preparation and Some Properties*, by R. A. Peters and R. W. Wakelin, November 1941.

h. Report No. 30 (V.15733). *Some Observations upon the Nature of the Compound of Mustard Gas with Keratin. Part II. Nitroprusside Reactions of the Keratin Preparations and some Thiethers*, by R. A. Peters and R. W. Wakelin, November 25, 1941.

i. Report No. 40 (V.20007). *On the Mechanism of the Physiological Action of Mustard. A Comparison of some Properties of Mustard and its Analogs*, by E. R. Holiday and A. G. Ogston, February 3, 1942.

j. Report No. 53 (W.4158). *Identification of Cysteine from the Products of the Splitting of a Thiether Linkage*, by R. A. Peters and R. W. Wakelin, May 11, 1942.

k. Report No. 57 (W.A2181Z). *Inhibition of Choline Esterase by T102 (S) or HN3*, by R. H. S. Thompson, June 1, 1942.

l. Report No. 68 (V.1663). *Serum Choline Esterase in Mustard Poisoning* (interim report), by R. H. S. Thompson, March 18, 1943.

m. V.9434. *The Respiration of Rat Skin after Damage with H*, by R. H. S. Thompson, July 22, 1940.

n. V.6437. *Investigations on the Vesicant Action of Mustard Gas*, by I. Berenblum, June 19, 1940.

o. V.20575B. *The Present Position of the Sulphone Theory*, by R. A. Peters, January 24, 1941.

p. V.22140. *A Summary of some Features of Work upon H since the Last War*, by R. A. Peters, E. Walker, I. Berenblum, J. Philpot, A. G. Ogston, and E. R. Holiday, February 4, 1941.

37. Cambridge Biochemical Laboratory (M. Dixon)

a. Report No. 1 (V.24815). *The Metabolism of Normal and Vesicant Treated Skin*, by D. M. Needham and M. Dixon, February 1941.

b. Report No. 2. *The Effect of Vesicants on Purified Pyruvic Oxidase*, by D. M. Needham and M. Dixon, February 1941.

c. Report No. 3. *The Action of H on Purified Enzymes*, by R. van Heyningen, February 1941.

d. Report No. 5 (V.800 B). *Hexokinase: A Vesicant Sensitive Enzyme*, by D. M. Needham, M. Dixon, and R. van Heyningen, March 1941.

e. Report No. 6 (V.800 A). *Effects of Some Non-vesicant Substances on Skin Metabolism and Enzyme Systems*, by M. Dixon and D. M. Needham, March 1941.

f. Report No. 7 (V.10355). *Studies on the Action of War Gases on Hormones. I. The Action of β,β'-dichlorethyl Sulphide on Insulin*, by M. Dixon, F. Danielli, D. M. Needham, and J. F. Mackworth, September 1941.

g. Report No. 9 (V.17203). *The Use of Frogs in Testing for Vesicant Activity*, by J. F. Danielli and N. Danielli, December 18, 1941.

h. Report No. 10 (V.17595). *The Properties and SH Nature of Hexokinase*, by R. van Heyningen, December 31, 1941.

i. Report No. 11 (V.17880). *Inhibition of Hexokinase and Skin Glycolysis as a Test for Vesicants*, by M. Dixon, R. van Heyningen, and D. M. Needham, undated.

j. Report No. 15 (W.12160). *The Effect of Vesicants on the Phosphokinases*, by D. M. Needham, October 1942.

k. Report No. 19 (V.7483). *The Phosphokinase Theory of Vesication, its Present Position*, by M. Dixon, June 21, 1943.

l. Report No. 21 (V.13244A). *Preliminary Experiments on the Mechanism of Systemic Poisoning by H*, by Jane Mackworth, September 16, 1943

m. Report No. 22 (V.13244B). *On the Mechanism of Systemic Poisoning by H*, by D. M. Needham, J. A. Cohen, and A. M. Barrett, September 16, 1943.

n. Report No. 31 (Z.12164). *The Action of H Sulphoxide on Tissues and Proteins* (*with an Appendix on the Action of Radio H on Normal Human Serum*, by T. E. Banks, J. C. Bournonll, G. E. Francis, C. Lutwak-Mann, K. Bailey, and E. C. Webb, November 6, 1944.

o. V.20575A. *Summary of Main Results of the Work of the Cambridge Biochemical Group*, by M. Dixon, January 4, 1941.

p. W.257. *Preliminary Report on the Biochemical Effects of S*, by D. M. Needham, R. Hill, R. van Heyningen, J. Mackworth, J. F. Danielli, J. Morgan, and M. Dixon, March 26, 1942.

q. W.257. *Biochemical Effects of S (HN2)*, by D. M. Needham, R. Hill, R. van Heyningen, J. Mackworth, J. F. Danielli, J. Morgan, and M. Dixon, April 4, 1942.

r. W.1258. *Addendum to Preliminary Report on S (HN2) from Cambridge Biochemical Laboratory*, by M. Dixon, June 22, 1942.

s. *Comments from London on Work on S (HN2)*, by M. Dixon, October 10, 1942.

38. Cambridge Biochemical Laboratory (A. Wormall)

a. Report No. 2 (V.15158A). *Action of H, H Sulphone, Divinylsulfide and Divinylsulphone on Amino Acids and Proteins*, by J. C. Bournonll, G. E. Francis, and A. Wormall, October 1941

b. Report No. 3 (V.15158B). *A Preliminary Note on the Action of H, H Sulphone and Divinylsulphone on Complement*, by J. C. Bournonll, G. E. Francis, and A. Wormall, October 1941.

39. Cambridge University, Strangeways Research Laboratory (H. B. Fell)

a. V.4558. *Report on the Biological Action of β,β'-dichlorpropylsulphide and T102 as Compared with Dichlorodiethylsulphide*, H. B. Fell and C. B. Allsopp, May 1941.

b. V.6718. *Report on Some Chemical and Biological Properties of the Product of the Interaction of H with Food Plasma*, by C. B. Allsopp and H. B. Fell, July 15, 1941.

c. W.257. *Provisional Interim Report on Some Physiological Properties of S*, by H. B. Fell, C. B. Allsopp, and J. F. Danielli, March 26, 1942.

d. W.19229. *Further Experiments on the Interaction between Plasma and Mustard Gas*, by C. B. Allsopp and H. B. Fell, October 1944.

40. Cambridge University (D. G. Cordier). C.D. Report No. 1071 (V.20361). *Studies on the Mechanism of Vesication made in the Bouchet Laboratories. I. Research on Hemolysis due to Chemical Warfare Agents which Generate Hydrochloric Acid by Hydrolysis. II. Research on the Cellular Toxic Action of Certain Chemical Warfare Agents, Generators of Hydrochloric Acid by Hydrolysis*, by D. G. Cordier, January 28, 1941.

41. Oxford Eye Hospital — Nuffield Laboratory of Ophthalmology (I. Mann)

a. V.1756. *Biochemical Study of the Effect of β,β'-dichlorethylsulfide on the Cornea*, by A. Pirie, April 26, 1941.

b. V.12478. *Further Report on the Reaction between β,β'-dichlorethylsulfide and Collagen from the Cornea*, by A. Pirie, October 7, 1941.

c. V.13008. *The Effect of H on the Activity of Hyaluronidase*, by A. Pirie, October 23, 1941.

42. University of Edinburgh (J. M. Robson)

a. W. 3079. *The Action of Mustard Gas in Ornamphilia. Production of Sterility and Mutations*, by C. Auerbach and J. M. Robson, June 1942.

b. V.14278. *The Action of H on the Pollen Grain Nucleus of Tradescantia*, by P. C. Koller, N. Y. Ansari, and J. M. Robson, October 16, 1943.

MISCELLANEOUS

43. V.3023. *A Short Statement upon the Present State of Knowledge upon the Biochemical Effects of H, H-sulphone, Chlorethylvinylsulphone and Divinylsulphone*, by I. Berenblum, F. Dickens, M. Dixon, D. Keilin, D. M. Needham, A. G. Ogston, R. A. Peters, J. Philpot, J. H. Quastel, and A. Wormall, March 24, 1941.

44. W.4334. *Notes on a Special Meeting of the Biochemical Group to Discuss Work on S*, by R. A. Peters, May 20, 1942.

45. W.4387. *Memorandum Concerning British Reports V.17929, V.17595 and V.17890*, by L. Hellerman, Carl F. Cori, and Vincent du Vigneaud, June 11, 1942.

CANADIAN REPORTS

Chemical Warfare Laboratories, Ottawa

46. Physiological Section Report No. 20. *Studies on the Immunological Behavior of H. I. Preparation of H Serum Protein Complexes*, by G. C. Butler, May 26, 1943.

Extramural Research

47. C.E. 44. University of Toronto, L. Young. Report 7. *I. The Action of Mustard Gas on Intestinal Phosphatase*, by Elizabeth A. MacPherson. *II. The Action of Mustard Gas on Yeast Phosphatase*, by Jules Tuba and C. W. Shen, June 25, 1942.

MISCELLANEOUS

48. *Proceedings of a Conference on Extramural Physiological Investigation Held in Ottawa, March 10, 1943*, p. 26, K. C. Fisher (Toronto).

OPEN LITERATURE

49. Bacq, Z. M. *Sur une Relation entre l'Inhibition de la Glycolyse et l'Action vésicante*. Enzymologia, **10**, 48-60 (1941).

50. Bacq, Z. M. and P. Augenot. *Inhibition d'une Fermentation lactique par des Vésicants dont certains Toxiques de Guerre*. Compt. rend. soc. biol., **134**, 105-107 (1940).

51. Bacq, Z. M. and M. Goffart. *Utilization of Ionic Potassium in the Investigation of Muscle Contraction after Work and Loss of Ability to Respond to a Stimulus (Landsgaard Effect)*. Compt. rend. soc. biol., **133**, 691 (1940). *Production of the Landsgaard Effect in Frog Muscles by Vesicants. Ibid.* **133**, 696 (1940). Cited from Chem. Abs., **34**, 7007.

52. Bacq, Z. M., Goffart, M. and Augenot, P. *Le Mode d'Action de certains Toxiques de Guerre et des Vésicants en general*. Bull. Acad. roy. Med. Belg. [6], **5**, 255-290 (1940).

53. Berenblum, I. *The modifying Influence of Dichlorethyl Sulphide on the Induction of Tumours in Mice by Tar*. J. Path. Bact., **32**, 425-434 (1929).

54. Berenblum, I. *The Anticarcinogenic Action of Dichlorethylsulphide (Mustard Gas)*. J. Path. Bact., **34**, 731-740 (1931).

55. Berenblum, I. *Experimental Inhibition of Tumor Induction by Mustard Gas and Other Compounds*. J. Path. Bact., **40**, 549-558 (1935).

56. Berenblum, I., L. P. Kinkal, and J. W. Orr. *Tumour Metabolism in the Presence of Anticarcinogenic Substances*. Biochem. J., **30**, 709-715 (1936).

57. Berenblum, I. and A. Wormall. *The Immunological Properties of Proteins Treated with β,β'-Dichlorethyl Sulphide (Mustard Gas) and β,β'-Dichlorethyl Sulphone*. Biochem. J., **33**, 75-80 (1939).

58. Flury, F. and H. Wieland. *Über Kampfgasverseifungen. VII. Die Pharmakologische Wirkung des Dichlorathylsulfids*. Z. ges. exp. Med., **12**, 307-183 (1921).

59. Laskowski, M. and L. Ryerson. *The Effect of Different Sodium Chloride Concentrations on Nuclei from Chicken Erythrocytes*. Arch. Biochem., **3**, 227-233 (1943-1944).

60. Lillie, R. S., G. H. A. Clowes, and R. Chambers. *On the Penetration of Dichlorethylsulphide (Mustard Gas) into Marine Organisms, and the Mechanism of its Destructive Action on Protoplasm*. J. Pharmacol. exp. Therap., **14**, 75-120 (1920).

61. Lynch, V., H. W. Smith, and E. K. Marshall, Jr. *On Dichlorethylsulphide. I. The Systemic Effect and Mechanism of Action*. J. Pharmacol. exp. Therap., **12**, 265-290 (1918).

62. Mirsky, A. E. and A. W. Pollister. *Nucleoproteins of Cell Nuclei*. Proc. Nat. Acad. Sci, US, **28**, 344-352 (1942).

63. Peters, R. A. *Effects of Dichlor-diethyl-sulfone on Brain Respiration*. Nature, **138**, 327-328 (1936).

64. Peters, R. A. and E. Walker. *Rate of Liberation of Acid by β,β'-Dichlorethyl Sulphide and its Analogues in its Relation to the "Acid" Theory of Skin Vesication*. Biochem. J., **17**, 260-276 (1923).

Chapter 22

OSRD FORMAL REPORTS

1. OSRD 276. *The Toxicity of β-Chloroethylthiocholine-Chloride*, by E. M. K. Geiling and F. C. McLean, University of Chicago Toxicity Laboratory, December 13, 1941. Div. 9-331.3-M1
2. OSRD 1107. *The Effects of Di-(β-chloroethyl)methylamine Hydrochloride on Renal Function in Rabbits*, by Betty Crawford and E. P. Hiatt, New York University, December 9, 1942. Div. 9-321.1-M1
3. OSRD 1131. *Summary of the Biochemical and Pharmacological Properties of the Amine Mustards*, by Homer W. Smith, New York University, December 9, 1942. Div. 9-321.1-M2
4. OSRD 1173. *The Pathology of Poisoning with Dichlorodiethylmethylamine*, by Clarence C. Lushbaugh, University of Chicago Toxicity Laboratory, February 3, 1943. Div. 9-321.1-M5
5. OSRD 1313. *A Study of the Hematological Changes Following Exposure to Certain War Gases*, by Clarence C. Lushbaugh, University of Chicago Toxicity Laboratory, April 3, 1943. Div. 9-385-M1
6. OSRD 1339. *The Clinical Pathology of Di-(β-chloroethyl)methylamine (TL 1/8)*, by David Karnofsky, Irving Graef, and Eleen Acklin, New York University, March 22, 1943. Div. 9-321.1-M8
7. OSRD 1391. *Toxic Effects of Compounds Related to Mustard. I. Toxic Effects of Mustard, Sesquimustard, and Sesquimustard Analogues*, by M. A. Lipton, S. Black, J. E. Lavalle, and C. C. Lushbaugh, University of Chicago Toxicity Laboratory, March 15, 1943. Div. 9-312.1-M2
8. OSRD 1717. *Review of the Literature on the Systemic Action of Mustard*, by Homer W. Smith, New York University, August ', 1943. Div. 9-312.14-M5
9. OSRD 3020. *The Mechanism of Cutaneous Injury by Mustard Gas. An Experimental Study Using Mustard Prepared with Radioactive Sulfur*, by F. C. Henriques, Jr., A. R. Moritz, H. S. Breyfogle, and L. A. Patterson, Harvard University, November 10, 1943. Div. 9-312.13-M4
10. OSRD 3306. *A Study of the Ability of Compounds with High Competitive Factors to Counteract the Injurious Effects of Mustard Gas*, by E. G. Ball, J. M. Buchanan, W. E. Doering, E. L. Marston, R. W. McKee, and R. A. Ormsbee, Harvard University, March 16, 1944. Div. 9-522.12-M15
11. OSRD 3407. *Studies on the Cause of Death after Systemic Intoxication with the β-Chloroethyl Vesicants*, by Homer W. Smith, Betty Crawford, and C. Riley Houck, New York University, April 12, 1944. Div. 9-321.1-M14
12. OSRD 3923. *A Study of the Composition of Blood and Urine of Rabbits and Rats as Affected by the Administration of H*, by E. G. Ball, E. H. Stotz, R. W. McKee, R. A. Ormsbee, and E. L. Marston, Harvard University, July 21, 1944. Div. 9-312.14-M6
13. OSRD 5146. *Final Report under Contract OEMsr-532*, by Barnett Cohen, Joseph Harris, E. R. Van Artsdalen, and Marie E. Perkins, Johns Hopkins University, May 20, 1945. Div. 9-200-M10
14. OSRD 5180. *The Comparative Systemic Effects of Mustard and the Nitrogen Mustards (HN1, HN2, HN3) in Rats*, by Irving Graef, Val B. Jager, and David A. Karnofsky, New York University, May 1, 1945. Div. 9-361.3-M2
15. OSRD 5245. *Effects of bis(β-Chloroethyl) Sulfide (H) and bis(β-Chloroethyl) Methylamine (HN2) on Enzymes In Vitro and In Vivo*, by C. F. Cori, S. P. Colowick, L. Berger, and M. W. Slein, Washington University School of Medicine, June 20, 1945. Div. 9-361.3-M3

OSRD INFORMAL REPORTS

16. Contract NDCrc-132, University of Chicago Toxicity Laboratory, E. M. K. Geiling. Inf. Month. Prog. Repts. on Toxicity of Chemical Warfare Agents: Div. 9-123-M1 Div. 9-123-M2
    a. Report (NDRC B4-A) of April 16, 1942.
    b. Report (NDRC B4-A) of May 16, 1942.
    c. Report (NDRC B4-A) of November 17, 1942.
    d. NDRC 9:4:1 No. 2, March 10, 1943.
    e. NDRC 9:4:1 No. 3, April 10, 1943.
    f. NDRC 9:4:1 No. 4, May 10, 1943.
    g. NDRC 9:4:1 No. 5, June 10, 1943.
    h. NDRC 9:4:1 No. 6, July 10, 1943.
    i. NDRC 9:4:1 No. 9, October 10, 1943.
    j. NDRC 9:4:1 No. 10, November 10, 1943.
    k. NDRC 9:4:1 No. 11, December 10, 1943.
    l. NDRC 9:4:1 No. 12, January 10, 1944.
    m. NDRC 9:4:1 No. 15, April 10, 1944.
    n. NDRC 9:4:1 No. 16, May 10, 1944.
    o. NDRC 9:4:1 No. 17, June 10, 1944.
    p. NDRC 9:4:1 No. 18, July 10, 1944.
17. Contract OEMsr-86, Harvard University, Eric G. Ball. Inf. Month. Prog. Repts. Div. 9-312.11-M1 Div. 9-312.14-M1
    a. Report (NDRC B4-C) of June 23, 1942.
    b. Report (NDRC B4-C) of October 28, 1942.
    c. Report (NDRC B4-C) of December 21, 1942.
    d. NDRC 9:5:1 No. 4, May 10, 1943.
18. Contract OEMsr-123, Washington University, Carl F. Cori. Inf. Month. Prog. Repts..
    a. Report (NDRC B4-C) of July 31, 1942. Div. 9-312.11-M1
    b. Report (NDRC B4-C) of August 28, 1942.
19. Contract OEMsr-129, The Rockefeller Institute for Medical Research, John H. Northrop. Inf. Month. Prog. Repts.:
    a. NDRC 9:5:1 No. 1, February 10, 1943. Div. 9-124-M4
    b. Personal communication from Roger M. Herriott, October 9, 1945.
20. Contract OEMsr-313, The Rockefeller Institute for Medical Research, Max Bergmann and Joseph S. Fruton. Inf. Month. Prog. Repts.:
    a. Report (NDRC B4-C) of May 23, 1942. Div. 9-124-M2 Div. 9-121-M5
    b. NDRC 9:5:1 No. 2, March 10, 1943.
    c. NDRC 9:5:1 No. 3, April 10, 1943.
    d. NDRC 9:5:1 No. 4, May 10, 1943.

e. NDRC 9:5:1 No. 5, June 10, 1943.
f. NDRC 9:5:1 No. 6, July 10, 1943.
g. NDRC 9:5:1 No. 8, September 10, 1943.
h. NDRC 9:5:1 No. 9, October 10, 1943.
i. NDRC 9:5:1 No. 11, December 10, 1943.
j. NDRC 9:5:1 No. 13, February 10, 1944.
k. NDRC 9:5:1 No. 14, March 10, 1944.
l. NDRC 9:5:1 No. 16, May 10, 1944.
m. NDRC 9:5:1 No. 17, June 10, 1944.

22. Contract OEMsr-434, The Rockefeller Institute for Medical Research, Philip D. McMaster and George H. Hegeman. Inf. Month. Prog. Rept. (NDRC B4-C) of August 28, 1942. Div. 9-124-M3

27. Contract OEMsr-532, The Johns Hopkins University, Barnett Cohen. Inf. Month. Prog. Rept. NDRC 9:5:1 No. 25, February 10, 1945. Div. 9-212.5-M3

28. Contract OEMsr-556, New York University, Homer W. Smith. Inf. Month. Prog. Repts: Div. 9-300-M1
a. Report (NDRC B4-C) of July 31, 1942.
b. Report (NDRC B4-C) of August 28, 1942.
c. Report (NDRC B4-C) of September 28, 1942.
d. Report (NDRC B4-C) of October 28, 1942.
e. Report (NDRC B4-C) of November 30, 1942.
f. Report (NDRC B4-C) of December 21, 1942.
g. NDRC 9:5:1 No. 1, February 10, 1943.
h. NDRC 9:5:1 No. 2, March 10, 1943.
i. NDRC 9:5:1 No. 3, April 10, 1943.
j. NDRC 9:5:1 No. 4, May 10, 1943.
k. NDRC 9:5:1 No. 5, June 10, 1943.
l. NDRC 9:5:1 No. 6, July 10, 1943.
m. NDRC 9:5:1 No. 7, August 10, 1943.
n. NDRC 9:5:1 No. 8, September 10, 1943.
o. NDRC 9:5:1 No. 9, October 10, 1943.
p. NDRC 9:5:1 No. 10, November 10, 1943.
q. NDRC 9:5:1 No. 11, December 10, 1943.
r. NDRC 9:5:1 No. 14, March 10, 1944.
s. NDRC 9:5:1 No. 15, April 10, 1944.
t. NDRC 9:5:1 No. 16, May 10, 1944
u. NDRC 9:5:1 No. 17, June 10, 1944.
v. NDRC 9:5:1 No. 18, July 10, 1944.
w. NDRC 9:5:1 No. 19, August 10, 1944.
x. NDRC 9:5:1 No. 20, September 10, 1944.
y. NDRC 9:5:1 No. 21, October 10, 1944.
z. NDRC 9:5:1 No. 22, November 10, 1944.
aa. NDRC 9:5:1 Unpublished results.

24. Contract NDCrc-169, Harvard University, A. R. Moritz and F. C. Henriques, Jr. Inf. Month. Prog. Rept. NDRC 9:5:1 No. 22, November 10, 1944. Div. 9-312.134-M3

25. Contract OEMcmr-24, The Johns Hopkins University, Alan C. Woods and Jonas S. Friedenwald. *Report to the Committee on Gas Casualties*, by J. S. Friedenwald, March 18, 1942. Div. 9-384-M2

26. Contract OEMcmr-51, Yale University, William T. Salter.
a. *Survey Report, Contract No. OEMcmr-51*, by W. T. Salter, April 17, 1942. Div. 9-522.12-M1
b. *Summary of Report of July 2, 1942*, by W. T. Salter.
c. Bulletin D, September 1, 1942. Div. 9-522.12-M3
d. Informal Prog. Rept. No. 22, December 1, 1942. Div. 9-522.12-M5
e. Inf. Prog. Rept. No. 20, June 16, 1943. Div. 9-522.2-M1
f. *The Acute Pharmacological Actions Elicited by the Intravenous Administration of 1130 and 1070 in the Form of their Hydrochloride Salts*, by Louis Goodman and Alfred Gilman, July 2, 1942.
g. *Pharmacodynamics of No. 1130 and its Transformation Products and the Antidotal Value of Sodium Thiosulfate*, by Alfred Gilman, Louis Goodman, and Frederick S. Philips, October 1, 1942. Div. 9-522.21-M1
h. *Toxicity of Water Contaminated with bis(β-Chloroethyl)methyl Amine (TL.148) and tris(β-Chloroethyl) Amine and Procedures for Decontamination*, by Alfred Gilman, Louis Goodman, and Frederick S. Philips with the assistance of Roberta P. Allen, December 16, 1942. Div. 9-321.1-M3
i. *The Pharmacodynamics of the Nitrogen Mustards*, by Alfred Gilman, Louis Goodman, and Frederick S. Philips with the assistance of Roberta P. Allen, February 19, 1943. Div. 9-321.1-M6
j. *Further Studies on the Toxicity of Orally Ingested TL.148 in Water. The Adequacy of the DB3 Test for the Detection of Toxic Concentrations of TL.148*, by Alfred Gilman, Louis Goodman, and Frederick S. Philips with the assistance of Roberta P. Allen, March 7, 1943. Div. 9-321.1-M7
k. *The Protective Effect of Various Ointments Against the Systemic Toxicity of Cutaneously Applied TL.145*, by Alfred Gilman, Louis Goodman, and Frederick S. Philips with the assistance of Roberta P. Allen, June 14, 1943. Div. 9-522.2-M1
l. *The Bone Marrow and Hemopoietic Effects in Mice of Small Repeated Parenteral Doses of TL.145 HCl*, by Thomas Dougherty, Louis Goodman, Alfred Gilman, and Jean Dougherty, October 5, 1943. Div. 9-321.1-M12

27. Contract OEMcmr-108, University of Pennsylvania, D. Wright Wilson and Harry M. Vars.
a. *Report on Work Done on the Wound Healing Project from April 20 to June 25, 1942.* Div. 9-322-M1
b. *The Toxicity of TL.145 in Tap Water. Minimum Concentration Causing Toxic Manifestations in Rats. The Uses of the DB3 Test for Determining Potability for Man*, by D. Wright Wilson, Samuel Gurin, Harry M. Vars, Dana L. Crandall, and William J. Brown, Jr., May 7, 1943. Div. 9-321.1-M9
c. *Studies of the Action of HMT on TL.148 in Vivo*, by Harry M. Vars, Samuel Gurin, William J. Brown, Jr., Dana Crandall, and Adelaide Delluva, September 20, 1943. Div. 9-322.2-M2
d. *Prophylactic Treatment of HN-2 Poisoning in Rats by Intubations with HMT*, by Harry M. Vars with technical assistance of L. J. Santamarin, E. Brown, and M. S. Mellett, January 15, 1944. Div. 9-322.2-M3
e. *Increased Tolerance of Rats Subjected to Repeated Exposure to HN Compounds*, by D. Wright Wilson, Harry M. Vars, with technical assistance of William J. Brown, Jr., L. Santamarin, and E. Bowen, September 9, 1944. Div. 9-321.1-M15

28. Contract OEMcmr-141, Harvard University, D. G. Cogan. Report No. 45. *Measurement of Rate of Reaction of H in Blood*, by W. Morton Grant, V. Everett Kinsey with the technical assistance of Phyllis Robbins, Helen Penta, and Helen Sullivan, January 2, 1945.
Div. 9-312.14-M7

29. Contract OEMcmr-96, Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, Cornelius P. Rhoads. Month. Prog. Rept. No. 10, January 31, 1943. Div. 9-523-M1

MISCELLANEOUS

30. NDRC Division 9 Informal Memorandum No. 1, *H Vapor. Summary of Data on Toxicology and Casualty Production*, by Homer Smith, New York University, March 1, 1944. Div. 9-312.1-M4

31. NDRC Division 9 Informal Memorandum No. 2, *Summary of Data on Q and Related Sesquimustards*, by Homer W. Smith, New York University, March 1, 1944.
Div. 9-312.1-M3

UNITED STATES ARMY REPORTS

Chemical Warfare Service

32. DPGSR 13. *Field Observations on the Physiological Effect of HN1*, August 23, 1943.

33. Dugway Proving Ground Chemical Warfare Service Mobile Field Unit, Bushnell, Florida. *Report on H Vapor Casualties Occurring at Bushnell, Florida, April 20, 1944*, June 6, 1944.

34. EAMRD 24. *The Chemical Action of Mustard within the Body*, October 10, 1924.

35. HR(EA) Rept. No. 1. *The Clinical Aspects of Exposure to Nitrogen Mustard (Compound No. 1139)*, June 17, 1943.

36. HR(EA) Rept. No. 2. *Idiosyncrasy to Nitrogen Mustard: No. 1139 (Report of a Case)*, June 30, 1943.

37. MD(EA)MR 53. *Toxicity of Mustard in the Rat Following Application to the Tail*, May 28, 1942.

38. MD(EA)MR 59. *Preliminary Report on Hematological Changes in the Rabbit Following Exposure to Lethal Doses of 1130*, June 30, 1942.

39. MD(EA)MR 63. *Some Pharmacological Effects of Compound Di-(β-chloroethyl)methyl Amine on Isolated Smooth Muscle*, August 7, 1942.

40. MD(EA)MR 64. *Preliminary Report on the Changes in Certain Constituents of the Blood of Rabbits Following Exposure to 1130*, August 11, 1942.

41. MD(EA)MR 68. *Therapy Directed to the Hematogenic System of Rabbits Burned with Lethal Applications of Compound 1130*, October 9, 1942.

42. MD(EA)MR 69. *The Pharmacological Action of Compound 1130*, October 27 1942

43. MD(EA)MR 78. *The Effects of Mustard on Muscle Tissue*, January 9, 1943.

44. MD(EA)MR 91. *The Concentration of Sugar in the Blood of Animals Exposed to Chemical Warfare Agents*, May 24, 1943.

45. Med. Div. Rept. No. 4. *The Effect of HN3 on Water and Electrolyte Balance in Dogs*, October 5, 1944.

46. Med. Div. Rept. No. 5. *Intravenous Nitrogen Mustard (HN3)*, October 28, 1944.

47. Med. Div. Rept. No. 27. *The Effects of H in Oil Applied to the Skin of Dogs*, March 20, 1945.

48. MR1(EA) Rept. No. 1. *The Oral Ingestion of 1070 by Humans*, September 16, 1943.

49. MR1(EA) Rept. No. 20. *Pathological Changes in Tissues of Victims of the Bari Incident*, May 18, 1944.

50. TDMR 423. *Tris(2-chloroethyl)amine. Physiological Examination*, August 12, 1942.

51. TDMR 630. *The Effect of Mustard and Lewisite on the Colloidal Gold Curve of Spinal Fluid*, May 4, 1943.

52. TDMR 666. *The Effects of Mustard on Peritoneal Tissue*, May 28, 1943.

53. TRLR 35. *Mustard (H): LCt50 of H to Goats — 10 Minute Exposure*, June 6, 1944.

54. Dugway Proving Ground Chemical Warfare Service Mobile Field Unit, Bushnell, Florida. Weekly Prog. Rept. Series 2 Rept. 68 part C, August 11, 1944.

55. Medical Division Inf. Month. Prog. Repts:
- a. October 1944.
- b. November 1944.
- c. December 1944.
- d. January 1945.
- e. February 1945.
- f. May 1945.
- g. July 1945.

56. Medical Research Laboratory, Edgewood Arsenal. Inf. Month. Prog. Repts.:
- a. October 15, 1943.
- b. December 15, 1943.
- c. February 15, 1944.
- d. April 15, 1944.
- e. May 15, 1944.
- f. June 15, 1944.
- g. July 15, 1944.
- h. August 15, 1944.
- i. September 15, 1944.

57. Contract W-49-057-CWS-23, University of Chicago Toxicity Laboratory, Inf. Month. Prog. Repts. on toxicity and irritancy of chemical agents:
- a. No. N.S. 1, April 10, 1945.
- b. No. N.S. 3, June 10, 1945.
- c. No. N.S. 4, July 10, 1945.
- d. No. N.S. 6, September 15, 1945.

58. Contract W-49-057-CWS-10, University of Virginia, Alfred Chanutin. Inf. Prog. Repts.:
- a. Rept. No. 1, August 15, 1944.
- b. Rept. No. 2, October 15, 1944.
- c. Rept. No. 3, December 15, 1944.
- d. Rept. No. 4, February 15, 1945.
- e. Rept. No. 5, April 15, 1945.
- f. Rept. No. 6, June 15, 1945.
- g. Rept. No. 7, August 15 1945.
- h. Rept. No. 8, October 15, 1945.

MISCELLANEOUS

59. *Toxic Gas Burns Sustained in the Bari Harbor Catastrophe*, by S. F. Alexander, Medical Corps, North African Theatre of Operations, December 27, 1943.

60. *Final Report of Bari Mustard Casualties*, by S. F. Alexander, Allied Force Headquarters, June 20, 1944.
61. *Report of an Informal Meeting on "The Systemic Effects of Mustard,"* Edgewood Arsenal, Md., 14 August 1945, Report to the Chief, Medical Division, CWS-CWS, September 14, 1945.

UNITED STATES PUBLIC HEALTH REPORTS

62. *Toxic Action of 2,2'-dichlorethyl Sulfide (Mustard Gas)*, by C. Voegtlin, et al., National Cancer Institute, National Institute of Health, U. S. Public Health Service, not dated.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

63. Porton Memorandum Report No. 15. *Classified List of Compounds Examined Physiologically Since 1919*, October 1941, and *Addendum I*, June 4, 1945.
64. Porton Memorandum No. 29 (Z.13290). *Interim Memorandum on Gas Warfare in the Tropics*, November 21, 1944.
65. Porton Report No. 2246. *Systemic Effects Induced by Mustard Gas Poisoning. First Report*, July 30, 1941.
66. Porton Report No. 2320. *Systemic Effects Produced by Mustard Gas Poisoning. Sedimentation Rate, Corpuscular Fragility, and Coagulation Time of Blood after Mustard Gas Poisoning, with a Note on Lewisite*, December 26, 1941.
67. Porton Report No. 2378. *Pathological Changes in Animals Exposed to S Vapour*, July 9, 1942.
68. Porton Report No. 2380. *Skin Application, Subcutaneous and Oral Administration of S*, June 22, 1942.
69. Porton Report No. 2383. *Third Report on Mustard Gas*, June 11, 1942.
70. Porton Report No. 2398. *Fourth Report on Mustard Gas. General Systemic Effects of Mustard Gas Applied to the Skin*, August 7, 1942.
71. Porton Report No. 2416. *The Chemistry of S and Related Compounds. Part I. The Preparation of S Chlorohydrin*, September 8, 1942.
72. Porton Report No. 2421. *The Toxicity of S in Water*, September 8, 1942.
73. Porton Report No. 2424. *S as a Water Contaminant*, September 8, 1942.
74. Porton Report No. 2460. *Blood Changes Due to S Derivatives*, December 1, 1942.
75. Porton Report No. 2462. *The Absorption of War Gases by the Nose in Rabbits*, December 12, 1942.
76. Porton Report No. 2483. *Chemical Studies on the Mode of Action of Mustard Gas on Proteins. Part I. The Nature of the Combination of H with Proteins*, February 19, 1943.
77. Porton Report No. 2496. *The Action of Water on T.773*, March 16, 1943.
78. Porton Report No. 2497. *Some of the Pharmacological Properties of S Hydrochloride*, April 5, 1943.
79. Porton Report No. 2503. *The Effect of S Hydrochloride and H on Gastric and Duodenal Secretion in the Cat*, April 29, 1943.
80. Porton Report No. 2516. *The Blood Picture of Rabbits Exposed to Low Concentrations of "H" for Long Periods*, May 31, 1943.
81. Porton Report No. 2523. *The Toxicity by Injection of Nitrogen Vesicants and Their Hydrolysis Products*, July 21, 1943.
82. Porton Report No. 2530. *Atropine Treatment of Animals Poisoned with H or S-Hydrochloride*, August 10, 1943.
83. Porton Report No. 2543. *Capillary Permeability Factors Related to the Action of CW Agents. Part I. Demonstration of the Presence of Such Factors in Certain CW Pathological Exudates*, September 21, 1943.
84. Porton Report No. 2548. *Toxicity and Pathology of HN-3*, November 18, 1943.
85. Porton Report No. 2551. *The Effect of Blood Transfusion on the Leucopenia Produced by HN-2 Hydrochloride*, October 12, 1943.
86. Porton Report No. 2562. *The Toxicity of HN-3 in Droplet Form*, November 17, 1943.
87. Porton Report No. 2587. *The Treatment of Systemic Effects of H. Part I. A Preliminary Survey of Therapeutic Agents of High Competition Factor*, March 10, 1944.
88. Porton Report No. 2596. *Toxicity of H in Droplet Form*, February 3, 1944.
89. Porton Report No. 2626. *The Treatment of the Leucopenia of Vesicant Poisoning*, June 20, 1944.
90. Porton Report No. 2635. *Capillary Permeability Factors Related to the Action of CW Agents. Part II. The Preparation and Partial Purification of Leucotaxine: Some Further Physiological Properties*, June 21, 1944.
91. Porton Report No. 2640. *The Effects of HN-2 Hydrochloride on the White Blood Cells and Lymphocyte Production in Dogs and Rabbits*, August 15, 1944.
92. Porton Report No. 2658. *The Treatment of Systemic Effects of H. II. Dithiocarbamates as Therapeutic Agents*, November 17, 1944.
93. Porton Report No. 2662. *The Treatment of Mustard Gas Intoxication with Plasma Transfusion. I. The Initial "Shock" Period*, December 13, 1944.
94. Porton Report No. 2680. *The Effect of Mustard Gas upon Biliary Fistula Animals*, May 29, 1945.
95. Porton Report No. 2681. *The Effect of a Protein Hydrolysate Upon Rabbits Poisoned with Mustard Gas*, May 18, 1945.
96. Ptn. 2800 (T.12752 and T.12908). *The Biochemical Mode of Action of Mustard Gas. A Review*, October 2, 1943.
97. Ptn. 2800 (T.672). *A Clinicopathological Report of Human Eyes Splashed with Mustard Gas*, February 3, 1944.
98. Phys. S R 123/43/PS. *Résumé of Medical Notes on W/Cmdr. Arthur Leslie Grice*, November 25, 1943 and December 3, 1943.
99. Phys. S R 148/43/PS. *Fatality Arising from a Mustard Explosion at Thorney Island* (W/O Hutchings), December 30, 1943.

Research Establishment, Sutton Oak

100. Y.11456. *Full Report on the T.773 Accident at Research Establishment, Sutton Oak, March 1943*, August 24, 1943.

101. Y.21305. *Severe H Contamination: Medical Report on John Hubert Hopkins. Toxic Vapour Casualties Due to S Vapour*, January 14, 1944.

Extramural Research

102. Cambridge Extramural Testing Station (E. D. Adrian)
   a. W.237. *Toxicity of S*, by M. Kilby, March 28, 1942.
   b. N2.61 (Y.3048). *General Toxicity on Injection of Certain Sulphones and of a Dithian Derivative*, by M. McCombie, B. A. Kilby, and M. Kilby, not dated.
   c. N2.128 (Y.5040). *The Inhibition of Acetylcholine Synthesis by Di(β-chloroethyl)methylamine Hydrochloride and by Arsenite*, by W. Feldberg, May 19, 1943.

103. Cambridge Biochemical Laboratory (M. Dixon and A. Wormall)
   a. Dixon Report No. 18 (Y.7286). *The Effect of H on the Heart Rate of the Rat*, by J. A. Cohen, June 1943.
   b. Dixon Report No. 22 (Y.13244B). *On the Mechanism of Systemic Poisoning by H*, by D. M. Needham, J. A. Cohen, and A. M. Barrett, September 16, 1943.
   c. Dixon Report No. 23 (Y.17077). *The Fate of Injected Radio-H in the Body*, by J. C. Bournsell, J. A. Cohen, G. E. Francis, and D. M. Needham, December 1943.
   d. Dixon Report No. 28 (Z.7463). *The Fate of Radio-H in the Body. II*, by T. E. Banks, J. C. Bournsell, G. E. Francis, C. L. Munn, and D. M. Needham, August 8, 1944.
   e. Dixon Report No. 29 (Z.9483). *The Fate of Injected Radio-H in the Body. III. Excretion in the Bile*, by T. E. Banks, J. C. Bournsell, G. E. Francis, and G. D. Greville, September 14, 1944.
   f. Dixon Report No. 31 (Z.12104). *The Action of H-Sulfoxide on Tissues and Proteins*, forwarded by the Chemical Board on November 6, 1944.
   g. Dixon Report No. 33 (Z.17189). *The Fate of Injected Radio-H in the Body. IV. Excretion in the Urine and Feces*, by T. E. Banks, J. C. Bournsell, G. E. Francis, and G. D. Greville, forwarded by the Chemical Board on February 24, 1945.
   h. Wormall Report No. 14 (Z.17190). *The Fate of Injected Radio-H in the Body. V. Further Observations on the Distribution of Radio-Sulfur in the Tissues*, by T. E. Banks, J. C. Bournsell and G. E. Francis, forwarded by the Chemical Board on February 22, 1945.
   i. Wormall Report No. 15 (A.5207). *The Fate of Injected Radio-H-Sulphone in the Body*, by T. E. Banks, J. C. Bournsell, and G. E. Francis, forwarded by the Chemical Board on August 10, 1945.

104. Cambridge University (D. G. Cowlier)
   a. V.3204. *Absorption Through the Skin, And Systemic Effects of Mustard Gas and Lewisite*, May 19, 1941.
   b. V.17044. *Action of the Vesicants on the Autonomic Nervous System. I. Atropine-like Effect of Vesicants of Nitrogen Group on the Cardio-vascular System. Relation Between the Chemical Constitution and Atropine-like Effect*, December 16, 1941.
   c. V.17921. *Action of the Vesicants on the Autonomic Nervous System. II. Physiological Study of Trichlorotriethylamine (Hydrochloride) Hydrolysis in Connection with Atropine-like Effect on the Heart*, December 30, 1941.
   d. V.18873A. *Physiological Studies on the Systemic Effects Induced by Mustard Gas Poisoning. I. Action on the Nervous System*, December 12, 1943.
   e. V.18873B. *Physiological Studies on the Systemic Effects Induced by Mustard Gas Poisoning. II. Action on the Cardio-vascular System*, January 1, 1944.
   f. V.20330. *Physiological Studies on the Systemic Effects Induced by Mustard Gas Poisoning. III. Effects of Certain Derivatives of Mustard Gas on the Cardio-vascular System and Discussion on the Mode of Action of H on This System*, January 25, 1944.
   g. Z.1008. *Physiological Studies on the Systemic Effects Induced by Mustard Gas Poisoning. IVa. Action on the Glands Adjoining the Digestive System — Salivary Glands*, August 25, 1944.
   h. Z.12169. *Physiological Studies on the Systemic Effects Induced by Mustard Gas Poisoning. IVb. Action on the Glands Adjoining the Digestive System: Influence on the External Secretion of the Pancreas and on the Secretion of Bile*, October 27, 1944.
   i. Z.18910. *Physiological Studies on the Systemic Effects Induced by Mustard Gas Poisoning. V. Tentatives of Therapy with Drugs Acting on Autonomic Effector Cells*, March 16, 1945.
   j. A.241. *Physiological Studies on the Systemic Effects Induced by Mustard Gas Poisoning. VI. Effect of Chemical Substances Related to Mustard Gas on Autonomic Effector Cells*, April 5, 1945.

105. Oxford University (R. A. Peters) — Department of Biochemistry
   a. Report No. 15 (C.13702). *Further Search for Thiol Antidotes to H (Mustard)*, by E. R. Holiday, A. G. Ogston, R. A. Peters, J. St. L. Philpot, and L. A. Stocken, September 24, 1940.
   b. Report No. 40 (V.15197A). *Preparation and Properties of β-hydroxyethyl-β'-chloroethyl sulphide (H chlorohydrin, H Half-hydrolysis Product, ClH)*, by A. G. Ogston, forwarded by the Chemical Board on November 17, 1941.
   c. Report No. 63 (W.15840). *The Significance of Cholinesterase Inhibition in Poisoning by Chemical Vesicants*, by R. H. S. Thompson, November 6, 1942.
   d. Report No. 68. (Y.1063). *Serum Cholinesterase In Mustard Gas Poisoning (Interim Report)*, by R. H. S. Thompson, March 19 1943.
   e. Research Item No. 21. (W.257). *Provisional Note Upon T1024*, by Holiday, Ogston, Stocken, Thompson, and Whittaker, March 27, 1942.

106. University College, Leatherhead (W. H. Newton)
   a. W.10338. *Some Effects of Mustard Gas on Motility and Secretions of the Alimentary Canal in Dogs and*

Cats. (First Progress Report), by R. A. Gregory and D. H. Smyth, not dated.

b. V.11940 and amendment V.12462. *A Note on the Effect of Application of H to the Gastric Mucosa of Dogs*, by R. A. Gregory and D. H. Smyth, forwarded by the Chemical Board on September 8, 1943.

c. Z.7168. *The Effect of Mustard Gas on Nitrogen and Chloride Excretion and Water Balance on the Partially Enterectomized Dog*, by R. A. Gregory and D. H. Smyth, forwarded by the Chemical Board on August 2, 1944.

d. Z.7169. *The Effect of H on the Level of Blood Calcium*, by D. H. Smyth, forwarded by the Chemical Board on July 29, 1944.

MISCELLANEOUS BRITISH REPORTS

107. New Red Book (C.D.R.D. Report on the Chemistry and Toxicology of Certain Compounds, 1940).

108. V.9698. Chemical Board Notes J184 to 188 of the Medical Sub-Committee Meeting held at the Ministry of Supply on July 29, 1941.

109. V.10557. Chemical Board Notes 8.12 to 8.15 of the Biochemical Subcommittee Informal Meeting held on July 1 and 2, 1943.

110 Z.11808. Chemical Board Physiological Subcommittee Notes F.661 to F.668. Meeting of October 12, 1944.

111. Z.3906. *Recent Work in the Pathology and Treatment of War Gas Poisoning*, issued by the Ministry of Supply, June 1944.

112. V.17345. *A Fatal Mustard Gas Casualty*, by A. R. Gordon, Canadian Military Headquarters, forwarded by the Chemical Board on December 6, 1943.

113. Voluntary Medical Report No. 3. *Mustard Gas Fatality at Newport (Mon.)*, forwarded by H. Southworth, February 18, 1943.

114. Voluntary Medical Report No. 47. *Gas Casualties in Scotland*, forwarded by H. Southworth, May 25, 1943. *Part II. Clinical Description of Accidental Mustard Gas Injuries in Glen Mervick House, Aberdeenshire, February 1943*, by R. S. Aitkin.

115. Voluntary Medical Report No. 59. *Fatal Case of Mustard Gas Poisoning at Fareham*, by H. Southworth, June 11, 1943 This includes a report from Porton dated April 10, 1943: Phys. S R 31 43 PS.

116. Cameron, G. R., Personal Communication to R. Kingan.

CANADIAN REPORTS

Experimental Station, Suffield, Alberta

117. Suffield Technical Minute No. 15. *The Toxicity of Orally Administered Aqueous Solutions of S-Base and S-Hydrochloride and the Effect of Treatment with Sodium Hydroxide*, January 8, 1943.

118. Suffield Technical Minute No. 92. *Vapour Damage from Gross Mustard Contamination (Field Experiment 141)*, October 8, 1943.

Chemical Warfare Laboratories, Ottawa

119. Physiological Section Report No. 5. *Effect of Subcutaneous Injections of S in Guinea Pigs, Preliminary Report*, June 16, 1942.

120. Physiological Section Report No. 9. *Toxicity of S and Related Compounds to Mice by Subcutaneous Injection*, August 13, 1942.

121. Physiological Section Report No. 33. *Toxicity Tests of H by Subcutaneous Injection for Mice Maintained under Different Conditions of Temperature and Humidity*, January 24, 1944.

122. Physiological Section Report No. 34. *A Study of Blood Chemistry of Goats Following Exposure to Mustard Gas*, February 1, 1944.

Extramural Research

123. Project C.E. 44, University of Toronto (L. Young)

a. Report No. 6. *A Study of the Action of Liquid Mustard Gas on the Rat*, by L. Young, February 28, 1942.

b. Report No. 8. (C.P. 26). *Biochemical Experiments with Mustard Prepared from Radioactive Sulphur. Report No. 2*, by L. Young, September 20, 1942.

c. Report No. 15. (C.P. 73). *The Toxicity of Mustard Gas by Intravenous Injection Into the Rat*, by J. A. McCarter, December 1944.

d. Report No. 16. (C.P. 74). *Biochemical Experiments with Mustard Gas Prepared from Radioactive Sulphur. IV. The Movement of Toxic Agents from the Site of Application of Mustard Gas to the Skin of the Rat*, by J. A. McCarter and L. Young, December 1944.

e. Report No. 17. (C.P. 75). *Biochemical Experiments with Mustard Gas Prepared from Radioactive Sulphur. V. The Systemic Distribution of S^{35} at Different Times After Application of Radioactive Mustard Gas to the Skin of the Rat*, by L. Young, J. A. McCarter, M. Edson, and E. Estok, December 30, 1944.

f. Related to C.E. 44: (C.P. 20). *The Action of Liquid "S" on the Rat. Interim Report No. 1*, by L. Young, G. E. Brackenbury, and J. A. McCarter, June 20, 1942.

g. Related to C.E. 44: (C.P. 28). *Effect Produced by the Application of Liquid S to the Skin of the Monkey. Report No. 2 on S*, by D. A. Irwin, G. E. Brackenbury, and L. Young, December 14, 1942.

124. C.P. 42. *The Effect on Open Wounds of Direct Contamination with HS*, by F. D. White, W. G. Brock, and J. W. Rennie, University of Manitoba, Winnipeg, Canada, November 1943.

125. C.P. 67. *The Toxicity of Ingested Mustard for Rats as Judged by Food Consumption, Body Weight, and Gross Symptoms*, by R. G. Sinclair, and R. Stupnyk, Queens University, Kingston, Ontario, September 1944.

126. C.P. 78. *Observations on the Systemic Action of H on Rabbits*, by F. D. White, W. G. Brock, J. W. Rennie, and D. W. Penner, University of Manitoba, Winnipeg, Canada, February 1945.

AUSTRALIAN REPORTS

127. *Chemical Warfare Physiological Investigations Carried out at Townsville, Queensland, January to February 1943*, by F. S. Gorrill, March 1943.

128. CD (Australia) Report No. 15. *The Differential White Count in Man Following Exposure to Mustard Vapor*, January 24, 1944.

129. CD (Australia) Report No. 20. *The Differential White Count in Man Following Exposure to Mustard Vapor. 2nd Report*, March 29, 1944.

130. CD (Australia) Report No. 37. *The Systemic Effects of Mustard Gas Under Tropical Conditions as Seen in Four Cases of Liquid Contamination*, May 8, 1944.

131. CD (Australia) Report No. 55. *A Clinical Analysis of a Series of Mustard Burns Occurring Under Tropical Conditions*, October 18, 1944.

132. CD (Australia) Note No. 21. *The Effects of Exposure to Mustard Vapor on the Blood Coagulation Time in Man*, May 23, 1944.

133. CD (Australia) Note No. 50. *Exposure of Subjects to Mustard Vapour Dosages of 50, 140, 125, and 220 mg. min. m³ Under Tropical Conditions*, 1945.

INDIAN REPORTS

134. CDRE (India) Report No. 255. *The Appearances and Treatment of Mustard Gas Burns of the Skin Under Indian Conditions*, July 15, 1943.

135. CDRE (India) Report No. 285. *Report on Two Cases of Severe Skin Burns from Mustard Gas Vapor Under Tropical Conditions in India*, Nov. 20, 1944.

OPEN LITERATURE

136. Drinker, C. K. and J. M. Yoffey, *Lymphatics, Lymph, and Lymphoid Tissue*. Harvard University Press, Cambridge, Mass., 1941, pp. 244 270.

137. Flury, F. and H. Wieland, *Ueber Kampfgasvergiftungen. VII. Die pharmakologische Wirkung des Dichlordiäthylsulfids*. Zeit. ges. exp. Med., **13**, 307 (1921).

138. Goodman, L. and A. Gilman, *The Pharmacological Basis of Therapeutics*. The MacMillan Company, New York, 1941, p. 489.

139. Hobbs, T. B., *Fatal Case of Mustard Gas Poisoning*. Brit. Med. J., 1944 (2), 300.

140. Kinkeyatter, V. H. *Acute and Chronic Toxicity of Triethanolamine*. J. Indust. Hyg. and Toxicol., **22**, 206 (1940).

141. Moorhead, T. G. *The Clinical Results of Poisoning by Mustard Gas*. Dublin J. Med. Sci., **147**, 1 (1919).

142. Selye, H. *Thymus and Adrenals in the Response of the Organism to Injuries and Intoxications*. Brit. J. Exp. Path., **17**, 234 (1936).

Chapter 23

OSRD FORMAL REPORTS

1. OSRD 451. *The Study of the Mechanism of the Physiological Action of Mustard by Means of Radioactive Mustard*. A. R. Moritz, F. C. Henriques, Jr., W. G. Schneider, and R. S. Halford; Harvard University March 10, 1942. Div. 9-312.134-M1

2. OSRD 653. *Effect of Detergents and Related Compounds on the Solubility and Rate of Solution of Redistilled Levinstein Mustard*. R. M. Herriott and M. L. Anson, The Rockefeller Institute for Medical Research, June 23, 1942. Div. 9-212.112-M3

3. OSRD 1248. *The Inactivation of Enzymes by Mustard Gas*. R. Keith Cannan, New York University, March 10, 1943. Div. 9-312.12-M1

4. OSRD 1377. *A Survey of Sulfur Compounds that have been Studied for Vesicant Activity*. R. C. Fuson, C. S. Marvel, C. C. Price, Emanuel Emsberg, R. E. Foster, R. D. Lipscomb, and B. C. McKusick, The University of Illinois, April 30, 1943. Div. 9-212.5-M1

5. OSRD 1825. *A Study of the "Fixed Mustard" in Skin Tissues*. R. A. Ormsbee and F. C. Henriques, Jr., Harvard University, September 20, 1943. Div. 9-312.134-M2

6. OSRD 1911. *Determination of the Distribution of H and L in Skin and Eye Tissues by Radio-autographic Techniques*. G. Hamilton and Dorothy Axelrad, University of California, October 15, 1943. Div. 9-312-M2

7. OSRD 3249. *Preparation and Testing of Substances as Neutralizing or Therapeutic Agents for H Burns*. Karl Folkers, R. F. Phillips, C. H. Shunk, Hans Molitor, and Samuel Kuna, Merck and Company, February 15, 1944. Div. 9-522.12-M13

8. OSRD 3260. *Induced Hypersensitivity to bis(β-Chloroethyl) Sulphide and to HAL in Guinea Pigs*. J. G. Kidd and Karl Landsteiner, The Rockefeller Institute for Medical Research, March 4, 1944. Div. 9-312.135-M1

9. OSRD 3302. *A Study of the Ability of Compounds with High Competition Factors to Counteract the Injurious Effects of Mustard Gas*. J. M. Buchanan, W. E. Doering, E. L. Marston, R. W. Mckee, and R. A. Ormsbee, Harvard University, March 16, 1944. Div. 9-522.12-M15

10. OSRD 3286. *Tests of Chloramnide-Containing Ointments for Protection and Decontamination of Human Skin Against Vesicants*. Joseph Savit, J. F. Thomson, Eugene Goldwasser, Peter Debruyn, and M. A. Bloom, University of Chicago Toxicity Laboratory, March 21, 1944. Div. 9-311-M2

11. OSRD 3437. *A. Investigation of Detergents or Decontaminants for Mustard Gas. B. Enzyme Studies and Other Chemical Studies Bearing Upon the Action of Certain Vesicants*. Leslie Hellerman, C. C. Porter, J. L. Irvin, C. A. Prestn, and Ann Lindsay, The Johns Hopkins University, April 4, 1944. Div. 9-522.12-M17

12. OSRD 3620. *The Mechanism of Cutaneous Injury by Mustard Gas. An Experimental Study Using Mustard Prepared with Radioactive Sulfur*. F. C. Henriques, A. R. Moritz, H. S. Greyfogle, and L. A. Patterson, Harvard University, May 9, 1944. Div. 9-312.13-M4

13. OSRD 3620-A. *Additional Studies Pertaining to the Mechanism of Cutaneous Injury by Mustard Gas. An Experimental Study Using Mustard Prepared with Radioactive Sulfur*. A. R. Moritz, F. C. Henriques, Jr., F. R. Dutra, and L. A. Paterson, October 25, 1945. Div. 9-312.13-M5

14. OSRD 3943. *Analysis of Variations in Size of Blister*

After Application of H. Sewall Wright, University of Chicago Toxicity Laboratory, July 27, 1944. Div. 9-312.136-M4

15. OSRD 3044. *A Vapor-Train Study of the Comparative Vesicancy of Mustard and Several Related Amines and Sulfides on Human Skin.* Simon Black, K. P. DuBois, and M. A. Lipton, University of Chicago Toxicity Laboratory, August 30, 1944. Div. 9-361.1-M1
16. OSRD 4176. *Status Report on Toxicity and Vesicant Tests of Compounds Referred to the University of Chicago Toxicity Laboratory.* Hoylande D. Young. October 3, 1944. Div. 9-300-M4
17. OSRD 4211. *Addition of Surface Active Agents to Mustard.* P. L. Salzberg, W. A. Lazier, and J. H. Werntz, E. I. duPont de Nemours and Company, October 3, 1944. Div. 9-212.11-M9
18. OSRD 4230. *The Benesh Micropipette.* William Bloom, John F. Thomson, Eugene Goldwasser, Joseph Savit, and Peter DeBruyn, The University of Chicago Toxicity Laboratory, October 9, 1944. Div. 9-371-M4
19. OSRD 4273. *A Summary of the Vapor Pressures and Volatilities of Compounds Studied at the University of Chicago Toxicity Laboratory Up to August 1, 1944.* C. E. Redemann, S. W. Chaikin, R. B. Fearing, D. Van Horsen, J. Savit, D. Benedict, and G. J. Rotariu, November 4, 1944. Div. 9-200-M8
20. OSRD 4400. *Protective and Therapeutic Agents for War Gases — Preparation of New Antidotes.* P. L. Salzberg, W. A. Lazier, M. W. Farlow, and W. J. Peppel, Chemical Department, E. I. duPont de Nemours and Co., December 14, 1944. Div. 9-522.12-M10
21. OSRD 4638. *Tests for Decontamination of Mustard and Nitrogen Mustards on Human Skin.* Eugene Goldwasser, P. P. H. DeBruyn, J. F. Thomson, and Joseph Savit, University of Chicago Toxicity Laboratory, January 27, 1945. Div. 9-522-M3
22. OSRD 4841. *Biochemistry of the Action of Sulfur-Containing Vesicants.* Vincent du Vigneaud, F. H. Carpenter, H. F. McDuffie, Jr., H. McKennis, Jr., D. B. Melville, J. R. Rachele, C. M. Stevens, and J. L. Wood, Cornell University Medical College, March 20, 1945. Div. 9-312.1-M6
23. OSRD 4852. *I. The Necrotizing Action of Certain Substances Related to Mustard Gas, H, or to the Nitrogen Mustards. II. A Comparison of the Vesicant Action Exerted on Human Skin by Mustard Gas, H, and by Mixtures of H with Wetting Agents or Solvents.* G. H. Hogeboom, P. D. McMaster, M. B. Sulzberger, R. L. Baer, and Abram Kanof, The Rockefeller Institute for Medical Research, March 25, 1945. Div. 9-361.1-M3
24. OSRD 4853. *The Development of Methods for Testing the Ability of Agents to Combat the Effects of Mustard Gas, H, and Other Vesicants Upon the Skin.* P. D. McMaster, G. H. Hogeboom, M. B. Sulzberger, R. L. Baer, and Abram Kanof, The Rockefeller Institute for Medical Research, March 24, 1945. Div. 9-522.12-M20
25. OSRD 4854. *A Search for Decontaminating and Treatment Agents for Skin Exposed to Mustard Gas, H.* P. D. McMaster, G. H. Hogeboom, M. B. Sulzberger, R. L. Baer, and Abram Kanof, The Rockefeller Institute for Medical Research, March 24, 1945. Div. 9-522.12-M21
26. OSRD 4855. *The Penetration of Vesicant Vapors into Human Skin,* Max Bergmann, J. S. Fruton, Calvin Columbie, S. M. Nagy, M. A. Stahmann, and W. H. Stein, The Rockefeller Institute for Medical Research, March 24, 1945. Div. 9-361.1-M2
27. OSRD 5020. *Changes in the Circulation and in the Permeability of Vessels Within and About Mustard Gas and Lewisite Lesions of Rabbit Skin,* P. D. McMaster and G. H. Hogeboom, The Rockefeller Institute for Medical Research, May 3, 1945. Div. 9-362-M4
28. OSRD 5027. *The Inhibition of Vesiculation in Mustard Gas, H, Lesions of Human Skin by B.A.L.,* by P. D. McMaster, George Hogeboom, M. B. Sulzberger, R. L. Baer, and Abram Kanof, The Rockefeller Institute for Medical Research, May 3, 1945. Div. 9-522.11-M5
29. OSRD 5032. *A Formal Analysis of the Action of Liquid Vesicants on Bare Skin,* by H. D. Landahl, University of Chicago Toxicity Laboratory, May 5, 1945. Div. 9-300-M2
30. OSRD 5160. *Observations on the Role of Water in the Susceptibility of Human Skin to Vesicant Vapors,* by Birdsey Renshaw, OSRD Division 9, June 1, 1945. Div. 9-361.1-M4
31. OSRD 5181. *The Penetration of Vesicant Vapors into Human Skin (Supplement to OSRD No. 4855),* by Max Bergmann, J. S. Fruton, S. M. Nagy, and W. H. Stein, The Rockefeller Institute for Medical Research, June 6, 1945. Div. 9-361.1-M5
32. OSRD 5194. *Tests for Vesicancy on Human Skin,* by J. F. Thomson, H. D. Young, Joseph Savit, Eugene Goldwasser, R. G. Murray, and Peter DeBruyn, University of Chicago Toxicity Laboratory, June 1, 1945. Div. 9-300-M3
33. OSRD 5245. *Effects of bis(β-Chloroethyl)Sulphide (H) and Bis(β-Chloroethyl) Methylamine (HN-2) on Enzymes in Vitro and in Vivo,* by C. F. Cori, S. P. Colowick, Louis Berger, and M. W. Slein, The Washington University School of Medicine, June 20, 1945. Div. 9-361.3-M3
34. OSRD 5070. *Protective and Therapeutic Agents for War Gases: Therapeutic Agents for Mustard and Nitrogen Mustards II,* P. L. Salzberg, W. A. Lazier, A. A. Pavlic, G. W. Rigby, and W. H. Vinton, January 10, 1946. Div. 9-522-M4

OSRD INFORMAL REPORTS

35. Contract NDCrc-132, University of Chicago Toxicity Laboratory. E. M. K. Geiling. Inf. Month. Prog. Repts. on *Toxicity of Chemical Warfare Agents* (NDRC 9.4-A and 9.4.1). Div. 9-125 M2
    a. Rept. of July 20, 1942.
    b. NDRC 9.4.1 No. 5, June 10, 1943.
    c. NDRC 9.4.1 No. 6, July 10, 1943.
    d. NDRC 9.4.1 No. 7, August 10, 1943.
    e. NDRC 9.4.1 No. 12, January 10, 1944.
    f. NDRC 9.4.1 No. 13, February 10, 1944.
    g. NDRC 9.4.1 No. 15, April 10, 1944.
    h. NDRC 9.4.1 No. 16, May 10, 1944.
    i. NDRC 9.4.1 No. 17, June 10, 1944.
    j. NDRC 9.4.1 No. 18, July 10, 1944.
    k. NDRC 9.4.1 No. 19, August 10, 1944.

l. NDRC 9:4:1 No. 20, September 10, 1944.
m. NDRC 9:4:1 No. 21, October 10, 1944.
n. NDRC 9:4:1 No. 22, November 10, 1944.
o. NDRC 9:4:1 No. 23, December 10, 1944.
p. NDRC 9:4:1 No. 24, January 10, 1945.

36. Contract OEMsr-325, California Institute of Technology. E. H. Swift and Carl Niemann. NDRC 9:3 Inf. Rept. No. 97. *Tables of the Physical Constants of Chemical Warfare Agents*, June 5, 1944. Div. 9-200-M7

37. Contract OEMcmr-24, The Wilmer Institute, Johns Hopkins University. Alan C. Woods and James S. Friedenwald.
a. Rept. No. 29. *The Persistence of HS in Corneal Tissue*, by A. C. Snell, Jr., January 22, 1943. Div. 9-312.131-M7
b. Rept. No. 33. *The Loosening of the Corneal Epithelium by Mustard and Other Agents*, March 30, 1943. Div. 9-312.131-M9
c. Rept. No. 39. *The Loosening of the Corneal Epithelium by Mustard. II. Effect of Temperature*, September 10, 1943. Div. 9-312.131-M10
d. Rept. No. 45. *The Loosening of the Corneal Epithelium: III. Further Studies and an Analysis of Previously Reported Findings*, November 30, 1943. Div. 9-312.131-M12
e. Rept. No. 54. *The Effect of Various Agents on the Adherence of the Corneal Epithelium*, June 10, 1944. Div. 9-384-M4
f. Rept. No. 55. *The Water Content of the Corneal Epithelium after Treatment with H and with Other Agents which Loosen the Epithelium*, June 17, 1944. Div 9-312.131-M15

38. Contract OEMcmr-51, Yale University. William T. Salter.
a. Bulletin A. *An Investigation of the Mode of Action and Therapy of Chemical Irritants*, March 4, 1942. Div. 9-312.2-M1
b. Bulletin D. September 1, 1942. Div. 9-522.12-M2
c. Report No. 21. *Progress Report on Tests of Possible Therapeutic Agents for H Burns on Skin*, December 31, 1942. Div. 9-522.12-M6
d. Report No. 24. *Percent of Free H Recoverable from Rabbit Skin after Various Intervals*, May 2, 1943. Div. 9-312.133-M1
e. Report No. 28. *Keratolytics, Caustics and "H" Burns*, May 10, 1943. Div 9-312.136-M1
f. Report No. 30. *The Rate of Evaporation of "H" from Liquid Drops on Rabbit Skin*, May 17, 1943. Div. 9-312.133-M2
g. Report No. 35. *Tests of Possible Therapeutic Agents for "H" Burns on Skin: Organic Compounds Containing Sulfur*, May 28, 1943. Div. 9-522.12-M7
h. *The Protective Effect of Various Ointments Against the Systemic Toxicity of Cutaneously Applied TL145*, June 14, 1943. Div. 9-522.2-M1
i. Report No. 46. *Time Factor in Decontamination with Modern Powders and Ointments*, November 15, 1943. Div. 9-522.12-M12

39. Contract OEMcmr-57, University of Chicago. E. S. Guzman Barron.
a. *The Effect of 1070 and 1130 on the Metabolism of Tissue Slices and some Enzyme Systems*, September 18, 1942. Div. 9-321.2-M1
b. *The Effect of TL145 and TL146 on the Metabolism of Tissues and on the Activity of Some Enzyme Systems*, December 18, 1942. Div. 9-321.1-M4
c. *Effect of BAL on Respiration and Glycolysis of H-Treated Rat Skin*, January 21, 1944. Div. 9-522.11-M3

40. Contract OEMcmr-82, Johns Hopkins University, Maurice Sullivan.
a. Report No. 1. March 1, 1942. Div. 9-371-M1
b. *Survey of Work Already Accomplished*, April 18, 1942. Div. 9 312.13-M2
c. *Studies of the Effects of HS on the Skin of the Rat. III. Observations on the Pattern of Cutaneous Injury in Normal Rats and the Determination of the Most Suitable Sites for Testing*, July 3, 1942. Div. 9-312.132-M1
d. *Studies of the Effects of HS on the Skin of the Rat. V. A Comparison of the Effect of HS on the Skin of Normal Rats and Rats Deficient in the Entire Vitamin B Complex Other than Thiamin*, July 24, 1942. Div. 9-312.132-M2
e. *Studies of the Effects of HS on the Skin of the Rat. VI. The Reactivation Phenomenon*, September 1, 1942. Div. 9-312.132-M3
f. *Studies on the Effects of H on the Skin of the Rat. VIII. The Lack of Influence of Massive Doses of Crystalline Vitamin B Supplements on the Extent and Healing Time of Cutaneous Injury*, January 9, 1943. Div. 9-312.132-M4
g. *Studies of the Effects of H on the Skin of the Rat. IX. A Comparison of the Injury in Fat Deficient and Normal Rats*, January 15, 1943. Div. 9-312.132-M5
h. *Studies of the Effects of H on the Skin of the Rat. X. Carbohydrate Deficiency*, January 21, 1943. Div. 9-312.132-M6
i. *Studies on the Effects of H on the Skin of the Rat. XI. Protein Deficiency*, January 26, 1943. Div. 9-312.132-M7
j. *Studies of the Effects of HS on the Skin of the Rat. XIII. A Comparison of the Microscopic Alterations Produced by the Applications of Small Amounts of HS and M-1*, March 9, 1943. Div. 9-312.132-M8
k. *Studies of the Effects of HS on the Skin of the Rat. XIV. Pyridoxine Deficiency*, March 17, 1943. Div. 9-312.132-M9
l. *Studies of the Effects of HS on the Skin of the Rat. XV. Riboflavin Deficiency*, March 17, 1943. Div. 9-312.132-M10
m. *Studies of the Effects of HS on the Skin of the Rat. XVI. The Effect of Feeding Para Amino Benzamide*, April 13, 1943. Div. 9-312.132-M11
n. *Studies of the Effects of HS on the Skin of the Rat. XVII. Pantothenic Acid Deficiency*, May 3, 1943. Div. 9-312.132-M12
o. *Studies of the Effects of HS on the Skin of the Rat. XVIII. Summary of the Results of Tests with Various Compounds*, May 21, 1943. Div. 9-312.132-M13

p. *Studies of the Effects of HS on the Skin of the Rat. XIX. Vitamin A Deficiency*, July 23, 1943. Div. 9-312.132-M14

q. *Studies of the Effects of HS on the Skin of the Rat. XX. Analysis of the Influence of Choline and Cystine*, September 1, 1943. Div. 9-312.132-M15

r. *Studies of the Effects of HS on the Skin of the Rat. XXI. The Effect of a Low Protein (Casein) Diet*, September 1, 1943. Div. 9-312.132-M16

s. *Studies of the Effects of HS on the Skin of the Rat, XXII. Experiments with Biotin Deficient Animals and an Evaluation of the Effect of Administering Biotin Concentrate to Normal Animals*, September 1, 1943. Div. 9-312.132-M17

t. *Studies of the Effects of HS on the Skin of the Rat. XXIII. Magnesium Deficiency*, September 1, 1943. Div. 9-312.132-M18

u. *Studies of the Effects of HS on the Skin of the Rat. XXIV. Observations on the Effect of Inanition*, September 1, 1943. Div. 9-312.132-M19

v. *Studies of the Effects of HS on the Skin of the Rat. XXV. The Effect of Treatment with Vitamin A*, September 1, 1943. Div. 9-522.12-M10

w. *Studies of the Effects of HS on the Skin of the Rat. XXVI. The Spreading Effect Produced by Flexion and Extension of an Extremity Immediately after the Application of the Vesicant to the Groin*, September 1, 1943. Div. 9-312.132-M20

41. Contract OEMemr-83, Yale University. Samuel C. Harvey.
    a. *Healing of Normal Wound of the Skin*, April 20, 1942.
    b. Monthly Progress Report dated June 29, 1942. Div. 9-530-M1
    c. Report dated September 1, 1942. Div. 9-530-M2
    d. Monthly Progress Report No. 8, February 1, 1943. Div. 9-530-M3
    e. Progress Report, April 10, 1943. Div. 9-530-M4
    f. Annual Report, July 1, 1943. Div. 9-530-M5
    g. Progress Report No. 12, December 1, 1943. Div. 9-514.2-M1
    h. Progress Report No. 13, March 10, 1944. Div. 9-514.2-M1
    i. Progress Report No. 14, *The Use of Pyruvic Acid in the Treatment of Burns*, May 2, 1944. Div. 9-514.1-M1

42. Contract OEMemr-97 and 98, May Institute for Medical Research (Cincinnati) Arthur Mirsky, *Studies with Vesicant Agents*, April 20, 1942. Div. 9-302-M1

43. Contract OEMemr-103, Cornell Medical College. D. P. Barr and M. B. Sulzberger.
    a. Survey Report of April 20, 1942. Div. 9-515-M1
    b. Report of June 30, 1942. Div. 9-522.12-M2
    c. Report of September 1, 1942. Div. 9-500-M1
    d. Report of November 20, 1942. Div. 9-500-M2
    e. *Orientation Experiments on Rabbits and Human Beings in Decontamination and in Protection Against both Liquid Mustard and Liquid Lewisite*, March 29, 1943. Div. 9-523.1-M1
    f. *Comparisons Between S-501 in Watery Suspensions, In Powder Vehicles and in the Standard Ointment Base in Both Early Decontamination and Protection of Rabbit and Human Skin against Mustard Burns*, April 8, 1943. Div. 9-511.3-M3
    g. Report No. B-2, *A. The Effects of Pressure Bandages on the Progress of Mustard Gas Lesions on Human Skin; B. Comparison of the Effects of Pressures Bandages with Boric Acid Ointment and 5% Sulfathiazole Ointment in the Treatment of Nine Day Old Ulcerative Liquid Mustard Gas Lesions on Human Skin*, August 27, 1943. Div. 9-522.12-M9
    h. Report No. B-3, *Comparison of Lesions Produced by 2.5 Milligrams of Mustard Gas on Human Skin When Applied (a) By Droplet From A-27 Gauge Needle and (b) by Spreading with a Small Disc (Dead-Tip)*, August 27, 1943. Div. 9-312.136-M2
    i. Report No. B-5, *Definitive (Late) Treatment of Vesicular Mustard Gas Lesions on Human Skin*, November 3, 1943. Div. 9-522.12-M11
    j. Report No. B-6, *Skin Tests with Dilutions of Mustard Gas and the Determination of Levels of Sensitivity in Normal Individuals and in Those Experimentally Exposed to Relatively Small Amounts of Liquid Mustard Gas*, November 15, 1943. Div. 9-312.136-M3
    k. Report No. B-7, *Experiments on the Inhibitory Effect of BAL on Vesication Produced with Liquid Mustard Gas*, January 3, 1944. Div. 9-522.11-M1
    l. Report No. B-11, *The Effects of the Successive Use of Chlorinating Ointment and BAL Ointment in the Decontamination and Treatment of Skin Sites Exposed to Liquid Mustard Gas*, January 17, 1944. Div. 9-522.11-M2
    m. Report No. B-13, *Definitive (Late) Treatment of Mustard Gas Lesions with Silver Nitrate ½% in Petrolatum*, March 9, 1944. Div. 9-522.12-M14
    n. Report No. B-15, *The Failure of BAL Ointment to Inhibit Vesication Produced by Heat and Tincture of Cantharides*, March 17, 1944. Div. 9-513.4-M1
    o. Report No. B-16, *Effects of Penicillin on Mustard Gas Lesions on Human Skin*, March 31, 1944. Div. 9-522.12-M16
    p. Report No. B-17, *The Decontamination of Skin Sites Exposed to Mixtures of Liquid Mustard Gas and Lewisite*, March 31, 1944. Div. 9-523.1-M2
    q. Report No. B-26, *Tests on the Sensitivity of Whites and Nisei to Mustard Gas and Lewisite (Including Tests for Allergic Sensitization to Mustard Gas Following Experimental Exposure)*, June 20, 1944. Div. 9-302-M2
    r. Report No. B-29, *The Effect of Applications of Pyruvic Acid Starch Paste on the Rate of Healing of Mustard Gas Lesions*, September 5, 1944. Div. 9-514.1-M2
    s. Report No. B-31, *Tests for Skin Sensitivity to Mustard Gas on Exposed Subjects and "Non-Exposed" Control Subjects*, November 2, 1944. Div. 9-312.136-M5
    t. Report No. B-32, *The Effect of Applications of Various Acids in Starch Paste on the Rate of Healing of Chemical Burns*, February 5, 1945. Div. 9-514.1-M1

u. Report No. B-33, *The Comparative Effects of Pyruvic Acid-Starch Paste and Blank Starch Paste in the Treatment of Chemical Burns*, February 10, 1945. Div. 9-514.1-M3

v. Report No. B-34, *The Relative Efficacy of Horse Serum Followed by Heat-Lamp and of Sulfadiazine Ointment in the Treatment of Chemical Burns*, February 12, 1945. Div. 9-515-M3

w. Report No. B-35, *The Effect of Slough Removal with Pyruvic Acid-Starch Paste on the Rate of Healing of Chemical Burns*, February 14, 1945. Div. 9-514.1-M4

x. Report No. B-36, *Pyruvic Acid Starch Paste Followed by Sulfadiazine Ointment Compared with Sulfadiazine Ointment Alone in the Treatment of Chemical Burns*, February 14, 1945. Div. 9-514.1-M5

y. Report No. B-37, *Comparative Effects of Dry Dressings and of Sodium Sulfadiazine Ointment Applied to Chemical Burns Subsequent to Treatment with Pyruvic Acid Starch Paste*, February 14, 1945. Div. 9-514.1-M6

z. Report No. B-38, *Further Experiments on the Treatment of Chemical Burns with Silver Nitrate 15% Ointment*, February 16, 1945. Div. 9-515-M4

aa. Report No. B-39, *Investigations on Vehicles to Replace Starch Paste in the Acid Treatment of Burns*, February 28, 1945. Div. 9-514.3-M1

bb. Report No. B-40, *The Effect of Pyruvic Acid Treatment on the Healing Rate of Standard Experimental Thermal Burns*, April 11, 1945. Div. 9-514.1-M7

cc. Report No. B-41, *The Comparative Effects of Applications of Phosphoric, Pyruvic, and Tartaric Acids on the Rate of Healing of Chemical Burns*, April 13, 1945. Div. 9-514.4-M2

dd. Report No. B-42, *The Comparative Effects of Applications of Phosphoric, Pyruvic and Tartaric Acids on the Rate of Healing of Thermal Burns*, April 17, 1945. Div. 9-514.4-M3

ee. Report No. B-43, *Comparison of the Course of Chemical and Thermal Burns Under Pyruvic Acid Starch Paste Treatment*, May 11, 1945. Div. 9-514.1-M8

ff. Report No. B-44, *Methods for Biologic and Laboratory Tests of Vehicles Proposed for Use in the Acid Treatment of Burns*, June 4, 1945. Div. 9-514.3-M2

gg. Report No. B-45, *The Comparative Effects of Pyruvic Acid Starch Paste and Blank Starch Paste in the Treatment of Thermal Burns*, June 5, 1945. Div. 9-514.1-M9

hh. Report No. B-46, *Investigations on Vehicles to Replace Starch Paste in the Acid Treatment of Burns*, June 7, 1945. Div. 9-514.3-M3

44. Contract OEMcmr-108, D. Wright Wilson and Harry M. Vars, *Studies on the Decontamination of Liquid Mustard on Human Skin*, July 21, 1943. Div. 9-522.12-M8

45. Contract OEMcmr-141, Harvard University, D. E. Cogan, Rept No 8, *Correlation of Rate of Reaction of HS and HS Intermediates within Corneal Tissue (In Vitro) with the effect Produced*, by D. E. Cogan, V. E. Kinsey, and W. M. Grant, December 24, 1942. Div. 9-312.131-M6

46. Voluntary Project, Yale University, H. S. Burr, *Electrometric Studies of Skin Burns*, March 7, 1942. Div. 9-383-M1

MISCELLANEOUS

47. M. B. Sulzberger, R. L. Baer, A. Kanof, and C. Lowenberg, *Skin Sensitization to Vesicant Agents of Chemical Warfare*, Chapter 2 (pages 16-66) of Volume III, *Skin and Systematic Poisons*, of the Fasciculus on *Chemical Warfare Medicine* prepared for the Committee of Medical Research of the Office of Scientific Research and Development by the Committee on Treatment of Gas Casualties of the Division of Medical Sciences of the National Research Council, 1945. Div. 9-110-M3

48. M. B. Sulzberger, R. L. Baer, and C. Lowenberg, *The O.S.R.D. Program for Testing Chloramide Containing Ointments for Their Relative Irritancy and for Their Relative Decontaminating and Protective Properties against Mustard Gas on Human Skin*, Chapter 3 (pages 67-99) of Volume III, *Skin and Systematic Poisons*, of the Fasciculus on *Chemical Warfare Medicine* prepared for the Committee on Medical Research of the Office of Scientific Research and Development by the Committee on Treatment of Gas Casualties of the Division of Medical Sciences of the National Research Council, 1945. Div. 9-110-M3

49. M. B. Sulzberger, R. L. Baer, and C. Lowenberg, *The Use of BAL and BAL Preparations in Combating Skin Damage by Lewisite and Other Arsenical Warfare Agents*, Chapter 4 (pages 100-179) of Volume III, *Skin and Systematic Poisons*, of the Fasciculus on *Chemical Warfare Medicine* prepared for the Committee on Medical Research of the Office of Scientific Research and Development by the Committee on Treatment of Gas Casualties of the Division of Medical Sciences of the National Research Council, 1945. Div. 9-110-M3

UNITED STATES ARMY REPORTS

Chemical Warfare Service

50. CWS Pharmacological Research Division Rept. No. 200. *Individual Variation in Susceptibility to Mustard Gas. II. The Military Importance of the Variation*, 1918.

51. EAMRD 9. *Blistering Concentration of Mustard Gas Vapors for Exposures from Five Minutes to Three Hours*, January 10, 1923.

52. EAMRD 24. *The Chemical Action of Mustard Within the Body*, October 10, 1924.

53. EAMRD 91. *Effect of Humidity on the Vesicant Action of Mustard Gas, M-1, Methylchloramine and Methyldifluoramine*, June 25, 1928.

54. EATR 248. *Beta-Chloroethyl Mercaptan. Part I. Preparation. Part II. Toxicity: Median Lethal Concentration for Mice and Vesicant Action on Man*, September 20, 1939.

55. EATR 292. *Pathology of Heat and Mustard Burns: A Comparison*, January 10, 1939.

56. HRE-A) 2 *Idiosyncrasy to Nitrogen Mustard (No. 1159)*, June 30, 1943.

57. MD(EA)MR 22. *The Determination by Biological Methods of the Length of Time Irritant Substances Remain Active in the Skin of Living Goats, Following Application of Mustard*, June 17, 1941.
58. MD(EA)MR 37. *The Treatment of Chemical Casualties. III. Mustard Injuries of the Skin Treated with Normal Amyl Salicylate and No. 82 Ointment*, March 14, 1942.
59. MD(EA)MR 48. *The Production of Vesicles on the Plantar Surfaces of the Feet of White Rats. Development of a Method for Applying Liquid Chemical Warfare Agents and Therapeutic Treatment Together with Illustration*, March 28, 1942.
60. MD(EA)MR 65. *Immediate Therapeutic Value of Calcium Polysulfide Solutions as Compared with Other Treatments for Liquid Mustard Burns on Man*, August 18, 1942.
61. MRL(EA) Report No. 3. *The Pathology of Mustard Burns of Human Skin*, September 30, 1943.
62. MRL(EA) Rept. No. 36. *Evaluation of Local Treatment of H Burns*, September 1, 1944.
63. San Jose Project Rept. No. 24. *Relative Sensitivity to Liquid Mustard Gas of Continental U. S. Troops and Puerto Rican Troops in a Tropical Climate*, October 27, 1944.
64. TDMR 188. *Value of Various Compounds in the Treatment of HS Lesions*, September 6, 1939.
65. TDMR 356. *New Compounds. Physical Constants of Certain Organic Compounds (Mustard Homologues)*, June 20, 1942.
66. TDMR 490. *The Effect of Relative Humidity and Temperature on the Vesicant Action of Liquid Mustard*, December 2, 1942.
67. TDMR 632. *Local Sensitization of Human Skin to HS by means of Sensitive Serum*, April 26, 1943.
68. TDMR 676. *Distribution and Rate of Penetration of Mustard in Skin*, June 5, 1943.
69. TDMR 730. *A Preliminary Study of the Effect of Wetting Agents on the Vesicant Power of H and L*, August 30, 1943.
70. TDMR 731. *The Value of Permeable Protective Shorts as a means of Reducing the Number of Casualties from Exposure to H Vapor. Gas Chamber Tests*, September 9, 1943.
71. TDMR 778. *Wetting Agents in Vesicants: the System H-H_2O-Alkaterge-C*, December 11, 1943.
72. TRLR 43. *The Comparative Physiological Effect of H on Negri and Caucasian Soldiers*, September 12, 1944.
73. Medical Division, Inf. Month. Prog. Repts.
    a. October 1944.
    b. November 1944.
    c. January 1945.
    d. February 1945.
    e. March 1945.
    f. April 1945.
    g. May 1945.
    h. September 1945.
74. MRL(EA) Inf. Month. Prog. Repts.
    a. August 15, 1943
    b. September 15, 1943.
    c. October 15, 1943
    d. December 15, 1943.
    e. April 15, 1944.
    f. May 15, 1944.
    g. June 15, 1944.
    h. July 15, 1944.
    i. September 15, 1944.
75. TRL(EA) Inf. Month. Prog. Repts.
    a. July 15, 1944.
    b. September 15, 1944.
76. University of Chicago Toxicity Laboratory Rept. No. 56. *The Effects of Temperature, Humidity, and Season on the Reactions of Human Skin to Mustard Vapor (Chamber Tests)*, November 30, 1945. (Work done under Chemical Warfare Service Contract W-49-057-CWS-23 and Bureau of Medicine, Navy Department, Research Division Project X576).
77. Contract W-49-057-CWS-23, University of Chicago Toxicity Laboratory. Inf. Month. Prog. Repts. on *Toxicity and Irritancy of Chemical Agents.*
    a. No. N.S. 2, May 15, 1945.
    b. No. N.S. 3, June 15, 1945.
    c. No. N.S. 9, February 15, 1946.

UNITED STATES NAVY REPORTS

Naval Research Laboratory

78. Report No. P-2219. *Chamber Tests with Human Subjects. III. Design, Operation and Calibration of a Chamber for Exposing Forearms to H Vapor*, January 22, 1944.
79. Report No. P-2304. *A Controlled Laboratory Experiment to Compare Lesions Resulting from Application of Mustard, Lewisite, and Nitrogen Mustards to the Skin of the Forearms of Humans*, September 1, 1944.
80. Report No. P-2464. *Chamber Tests with Human Subjects. V. Arm Chamber Exposures to HN Vapors*, March 1945.
81. Report No. P-2570. *Chamber Tests with Human Subjects. IX. Basic Tests with H Vapor*, August 14, 1945.
82. Report No. P-2734. *Chamber Tests with Human Subjects. XVIII Tests with HN Vapors*, January 9, 1946.

UNITED STATES PUBLIC HEALTH SERVICE REPORTS

83. *Toxic Action of β,β'-Dichlorethyl Sulfide (Mustard Gas)*, by Carl Voegtlin and others, National Cancer Institute, National Institute of Health, United States Public Health Service, undated (received by NDRC on August 30, 1943).

UNITED STATES UNITED KINGDOM REPORTS

Project Coordination Staff (Edgewood Arsenal)

84. PCS Rept. No. 7. *Status Summary on the Relative Values of H, HN1, and HN3 as Bomb Fillings*, December 7, 1944.
85. PCS Rept. No. 9. *Resumé of Recent Knowledge on the Technical Aspects of Chemical Warfare in the Field*, May 17, 1945.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

86. *Porton Memorandum No. 15. Classified List of Compounds Examined Physiologically Since 1918*, October 1941, and Addendum 1, June 4, 1945.
87. Porton Report No. 483. *The Effects of the Vapor of H on the Human Skin*, May 31, 1927.
88. Porton Report No. 930. *Sensitivity to Mustard Gas*, July 22, 1931.
89. Porton Report No. 948. *Further Report on Sensitivity to Mustard Gas*, September 23, 1931.
90. Porton Report No. 2225. *The After-Treatment of Mustard Gas Injury to the Skin of Horses*, June 17, 1941.
91. Porton Report No. 2429. *The Relative Insensitivity to Mustard Gas of the Skin of the Hand*, September 21, 1942.
92. Porton Report No. 2483. *Chemical Studies on the Mode of Action of Mustard Gas on Proteins. Part I. The Nature of the Combination of H with Proteins*, February 19, 1943.
93. Porton Report No. 2518. *The Prevention of Vesication*, July 20, 1943.
94. Porton Report No. 2522. *The Treatment of Mustard Gas Blisters*, July 20, 1943.
95. Porton Report No. 2543. *Capillary Permeability Factors Related to the Action of CW Agents. Part I. Demonstration of the Presence of Such Factors in Certain CW Pathological Exudates*, September 21, 1943.
96. Porton Report No. 2610. *Early Changes Produced in the Skin of Animals by H*, April 14, 1944.
97. Porton Report No. 2631. *New Active Constituents for Anti-Gas Ointments*. Part I. Competitors. July 20, 1944.
98. Porton Report No. 2635. *Capillary Permeability Factors Related to the Action of CW Agents. Part II. The Preparation and Partial Purification of Leucotaxine: Some Further Physiological Properties*, July 21, 1944.
99. Porton Report No. 2637. *New Active Constituents for Anti-Gas Ointments. Part II. p-Alkoxy Derivatives of Chloramine-B*, July 21, 1944.
100. Porton Report No. 2647 *The Mode of Penetration of the Skin by Mustard Gas*, September 8, 1944.
101. Porton Report No. 2691. *An Experimental Study of the Effects of Applying Pressure to H Burns*, July 3, 1945.
102. Ptn. 1200 (R.9045). *Vesicancy of Halogenated Sulphones etc.*, July 23, 1941.
103. Ptn. 1230 (R.12035 and R.14727). *Comparative Vesicant Properties of Vesicant Compounds*, December 19, 1941.
104. Ptn. 1001A (V.1358). *Effects of H Vapor on Man*, February 7, 1945.
105. Ptn. 1753 (S.2867) *Report on the Physiological Examination of 18 Samples β-Chloroethyl Sulphides*, March 6, 1942.
106. Ptn. 2800-4 (T.10278). *Skin Responses to Diluted Mustard Gas*, August 4, 1943.
107. Ptn. 2800 (T 12752 and attachment T.12998). *The Biochemical Mode of Action of Mustard Gas: A Review*, October 2, 1943.

Research Establishment, Sutton Oak

108. S.O. R. 683. *Vesicant Action and Molecular Structure*, October 18, 1943.

Extramural Research

109. Cambridge Biochemical Laboratory (M. Dixon and A. Wormall)
   a. Dixon Report No. 1 (V.24815). *The Metabolism of Normal and Vesicant Treated Skin*, D. M. Needham and M. Dixon, February 1941.
   b. Dixon Report No. 8 (V.10548). *Studies on the Mechanism of Blister Formation*, J. F. Danielli and M. Danielli, forwarded by the Chemical Board on September 8, 1941.
   c. Dixon Report No. 9 (V.17203). *The Use of Frogs in Testing for Vesicant Activity*, J. F. Danielli and Mary Danielli, December 18, 1941.
   d. Dixon Report No. 11 (V.17800). *Inhibition of Hexokinase Skin Glycolysis as a Test for Vesicants*. M. Dixon, R. van Heyningen, and D. M. Needham, not dated.
   e. Dixon Report No. 14 (W.6703) *Some Effects of H on Skin Metabolism (With an Appendix on the Mechanism of Glycolysis)*, D. M. Needham and M. Dixon, forwarded by the Chemical Board on July 22, 1942.
   f. Dixon Report No. 19. (Y.7483). *The Phosphokinase Theory of Vesication; Its Present Position*. M. Dixon, forwarded by the Chemical Board on June 21, 1943.
   g. Dixon Report No. 30. (Z.9716). *The Action of H on Enzymes and Proteins*. K. Bailey, T. E. Banks, J. C. Bournsell, G. E. Francis, and E. C. Webb, September 21, 1944.
   h. V.18058. *Progress Report October 1939-October 1940*. A. Wormall, circulated by the Chemical Board on December 19, 1940.

110. Cambridge University Strangeways Research Laboratory (H. B. Fell)
   a. NU.6530. *A Histological Study of the Penetration and Spread of Dichlorethyl Sulphide in Tissues in Vitro and in Vivo*. H. B. Fell, not dated.
   b. V.6713. *Report on Some Chemical and Biological Properties of the Product on Interaction of β,β'-Dichlorodiethylsulphide with Fowl Plasma*. C. B. Allsopp and H. B. Fell, July 1941.
   c. NY.9106 and correction Y.10938. *The Effect on the Skin of Mice of Repeated Applications of Minute Quantities of Mustard Gas*. H. B. Fell and C. B. Allsopp, July 1943.

111. Oxford Eye Hospital - Nuffield Laboratory of Ophthalmology (I. Mann). V.21043. *Biological Properties of H Collagen, Together with a Discussion on the Production of Hypersensitivity by Simple Substances*. A. Pirie and B. D. Pullinger, forwarded by the Chemical Board on February 14, 1942.

112. Oxford University — Dyson-Perrins Laboratory (A. H. Ford-Moore). Y.11724. *The Assessment of Vesicant Power*, August 28, 1943.

113. Oxford University Department of Biochemistry (R. A. Peters)
   a. Report No. 2. *The Relation Between Toxicity to the Pyruvate Oxidase Enzyme System and Vesicant Action*, by R. A. Peters and R. W. Wakelin. January 1940.

b. Report No. 7. (V.3284). *Further Study of Possible Antidotes to H (Mustard)*, by E. R. Holiday, A. G. Ogston, J. St. L. Philpot, and L. Stocken, May 4, 1940.

c. Report No. 18 (addendum). *Disappearance of H Applied to Human Skin*, by E. R. Holiday and A. G. Ogston, March 25, 1941.

d. Report No. 28. (V.20065). *Effect of Substances Other than H Upon Some Dehydrogenases*, by R. A. Peters and R. Wakelin, February 3, 1941.

e. Report No. 39, Part I. (V.14978). *Observations Upon the Nature of the Compound of Mustard Gas with Keratein. Part I. Preparation and Some Properties*, by R. A. Peters and R. W. Wakelin, November 1941.

f. Report No. 39, Part II. (V.15733). *Some Observations Upon the Nature of the Compound of Mustard Gas with Keratein. Part II. Nitroprusside Reactions of the Keratein Preparations and Some Thio Ethers*, by R. A. Peters and R. W. Wakelin, forwarded by the Chemical Board on November 25, 1941.

g. Report No. 49. (V.20007). *On the Mechanism of the Physiological Action of Mustard: a Comparison of Some Properties of Mustard and Its Analogs*, by E. R. Holiday and A. G. Ogston, January 1942.

h. Report No. 50. (V.20058). *The Treatment of Mustard Gas Contamination with DTH*, by R. H. S. Thompson, January 8, 1942.

i. Report No. 51. (V.20444). *Preliminary Report on the Successful Hypersensitization of the Skin of Guinea Pigs to Mustard Gas*, by E. R. Holiday, February 1942.

j. Report No. 53. (W.4454/A). *The Splitting of the Thiaether Linkage in Certain Derivatives of Mustard*, by A. H. Ford-Moore, R. A. Peters, and R. W. Wakelin, May 11, 1942.

k. Report No. 59. (W.5217). *Cross Reactions in Guinea Pigs Hypersensitized to H*, by E. R. Holiday, June 10, 1942.

l. Report No. 62. (W. 8399). *Treatment of Mustard Burns with N-di-chloroethanesulphonamide*, by L. A. Stocken, July 18, 1942.

m. Report No. 67 (W.15840). *The Significance of Cholinesterase Inhibition in Poisoning by Chemical Vesicants*, by R. H. S. Thompson, November 6, 1942.

n. Report No. 72 (V.10508). *The Influence of Certain Dithio Compounds Upon Toxicity of Some Vesicants to the Pyruvate Oxidase System in Vitro*, by R. A. Peters and R. W. Wakelin, June 1943.

o. Report No. 80. (V.5791). *Skin Penetrance and Mustard Gas*, by A. Beloff, R. A. Peters, and R. Wakelin, July 1945.

p. V.6437 and addenda V.8199 and V.8136. *Investigations on the Vesicant Action of Mustard Gas*, by I. Berenblum, June 19, 1940.

q. V.9434. *The Respiration of Rat Skin After Damage with H*, by R. H. S. Thompson, July 22, 1940.

r. V.22140. *A Summary of Some Features of Work Upon H Since the Last War*, by R. A. Peters and Associates, February 4, 1941.

s. Z.7461. *Further Observations of Hypersensitivity to H in Guinea Pigs*, by E. R. Holiday, July 1944.

t. Z.8310. *A Note by Professor Peters on His Investigation on the Attempted Removal of Combined Mustard, Together with Some Comments on the American Work*, July 1944.

u. A.472. *Effect of Hydrogen Peroxide Upon the Stability of the Compound of Mustard Gas with Keratein*, by R. A. Peters and R. W. Wakelin, forwarded by the Chemical Board on April 14, 1945.

114. University of Edinburgh (G. A. Levvy). Y.21311. *The Effect of BAL on the Arsenic Content of Skin Contaminated with Arsenical Vesicants*, by A. F. Graham and A. C. Chance, February 16, 1941.

MISCELLANEOUS

115. CW Report 202. *Report on Comparison of Heat Burns and Scalds with Burns Produced by Mustard Gas Solution*, by H. R. Dean and M. B. R. Swann. Not dated.

116. V.13630. *The Rate of Disappearance of Dichlorlethylsulphide from the Skin, and Its Relation to the Mustard Gas Sensitivity of Different Species*, by G. Ungar (work carried out in France), forwarded by the Chemical Board on October 24, 1941.

117. W.257. Compilation, Apparently by L. T. D. Williams, of Reports by Four Extramural Teams:

a. *Provisional Interim Report on Some Physiological Properties of S*, by H. B. Fell, C. B. Allsopp, and J. F. Danielli, March 26, 1942.

b. *Preliminary Report on the Biochemical Effects of S*, by D. M. Needham, R. Hill, R. van Heyningen, J. Mackworth, J. F. Danielli, J. Morgan, and M. Dixon.

c. *Provisional Note Upon T.1024*, by R. A. Peters, March 27, 1942.

d. Note on the Toxicity of S, from M. Kilby to L. T. D. Williams, Containing Data in Addition to Those Reported on March 23, 1942. March 28, 1942.

118. Z.6438. Folio 227. *Report on Clinical Observations of the Healing and Treatment of Mustard Gas Blisters in the Middle East*, by S. Curwen, No. 2 Anti-Gas Laboratory, R. E., June 14, 1944.

CANADIAN REPORTS

Experimental Station, Suffield, Alberta

119. Suffield Technical Minute No. 72. *A Comparison of the Erythema and Vesicle Producing Capacity of HT MM and HT*, September 15, 1944.

120. Suffield Technical Minute No. 89. *Comparison of the Relative Vesicancy of HTV CR, HTV MM, and HTV CR MM*, March 3, 1945.

121. Suffield Technical Minute No. 103. *Effectiveness of Given Cts of Mustard Gas Vapour for Lung Exposure Periods Under Tropical Conditions*, August 13, 1945.

122. Suffield Field Rept. No. 133. *The Physiological Effects of Mustard Vapor at Low Temperatures*, August 9, 1945.

Chemical Warfare Laboratories, Ottawa

123. Physiological Section Rept. No. 20. *Studies on the Immunological Behavior of H. I. The Preparation of H-Serum Protein Complexes*, May 26, 1943.
124. Physiological Section Rept. No. 27. *Observations on the Treatment of Experimentally Produced Mustard Lesions*, December 21, 1943.
125. *Studies on the Immunological Behavior of H. II. The Production of Immune Bodies by the Use of H-Serum Protein Complexes*, Physiological Section Rept. No. 35, February 22, 1944.
126. *Studies of H Sensitivity in the Guinea Pig*, Physiological Section Report No. 39, May 22, 1944.
127. *The Reaction of H with Serum Proteins in the Presence of Phosphate*, Physiological Section Report No. 46, November 9, 1944.
128. *Studies of H Sensitivity in the Guinea Pig. II.* Physiological Section Rept. No. 48, February 5, 1945.
129. *Annotated Bibliography of the Penetration of Substances Through Skin*, Physiological Note No. 26, March 10, 1943.
130. *Note on an Unusual Case of Remote Response to Mustard Contamination*, Physiological Section Note No. 28, April 16, 1943.
131. *Notes on the Response of Hairless Mutants of the Mouse to Mustard Contamination*, Physiological Note No. 36, July 24, 1944.

Extramural Research

132. C. E. 44, University of Toronto (L. Young)
    a. *Biochemical Experiments with Mustard Gas Prepared from Radioactive Sulphur. Report No. 2.* Report No. 8 (C. P. 26). L. Young, September 20, 1942.
    b. *Biochemical Experiments with Mustard Gas Prepared from Radioactive Sulphur. III. The Local Distribution of Mustard Gas and Products Derived from It Following Its Application to the Skin of the Rat*, Report No. 9. (C. P. 37). S. J. Patrick, L. Young, M. Edson, and E. Estok, August 25, 1943.
133. C.E. 86, University of Toronto (G. F. Wright). Progress Report No. 6 (March 15 June 15, 1942). *Action of Aldehydes on Vesication by H*, by G. F. Wright and H. H. Richmond.
134. C.D. (Australia) Report No. 40. *Effect of Varying Humidity and Temperature Upon the Sensitivity of Human Skin to Mustard Vapor*, May 22, 1944.
135. C.D. (Australia) Report No. 41. *Effect of Varying Activity of Subjects During Exposure on the Sensitivity of Human Skin to Mustard Vapor*, May 19, 1944.
136. C.D. (Aust.) Rept. No. 42. *Assessment of Casualties from Vesicant Agents*, May 20, 1944.
137. C.D. (Australia) Report No. 55. *A Clinical Analysis of a Series of Mustard Burns Occurring Under Tropical Conditions*, October 18, 1944.
138. C.D. (Aust.) Rept. No. 78. *A Further Comparison Between Physiological Effects of Mustard Vapour in the Chamber and in the Field*, May 25, 1945.
139. C.D. (Aust.) Rept. No. 79. *A Scoring System for Mustard Vapour Burns*, June 5, 1945.
140. C.D. (Australia) Rept. No. 83. *The Early Progress of Mustard Vapor Burns Under Tropical Conditions*, July 2, 1945.
141. C.D. (Australia) Report No. 85. *Estimation of the Dose-Lesion Relationship for Human Exposure to Mustard Vapour*, February 28, 1946.
142. C.D. (Aust.) Note No. 50. *Exposure of Subjects to Mustard Vapour Dosages of 50, 150, 125 and 220 mg. mins. /m³ under Tropical Conditions*, 1945 but undated.
143. C.D. (Aust.) Note No. 56. *The Effect of Cumulative Exposures to Mustard Vapour*, July 2, 1945.

INDIAN REPORTS

144. CIDRE (India) Report No. 245. *The Effect of Mustard Vapor on the Skin Under Hot Weather Conditions*, December 17, 1942.

OPEN LITERATURE

145. Berenblum, I. *Experimental Inhibition of Tumour Induction by Mustard Gas and other Compounds.* J. Path. Bact., **40**, 549–558 (1935).
146. Berenblum, I., L. P. Kendal and J. W. Orr. *Cl Tumour Metabolism in the Presence of Anti-carcinogenic Substances. Biochem. J.*, **36**, 709–715 (1936).
147. Berenblum, I., and Wormall, A. *The Immunological Properties of Proteins Treated with β,β'-dichlorodiethyl Sulfide (Mustard Gas) and β,β'-dichlorodiethyl Sulfone. Biochem. J.*, **33**, 75–80 (1939).
148. Brunt, D. *The Reactions of the Human Body to Its Physical Environment.* Quart. J. Roy. Meteorological Society, **69**, 77–124.
149. Brunt, D. *Climate, Weather, and Man.* Endeavour 3, No. 2.
150. Claude, A. *Spreading Properties of Leech Extracts and the Formation of Lymph.* J. exp. Med., **66**, 353–366 (1937).
151. Ferri, G. *Recherche sulla sensibilita individuale della cute umana all'iprite e sopra alcuni fattori capaci di modificarla.* G. Med. milit., **88**, 919–933 (1937); abstracted in Zbl. Haut- u. Geschl Kr., **58**, 366 (1938) (quoted from reference 47).
152. Fries, Amos A. and Clarence J. West. *Chemical Warfare*, 445 pp. McGraw Hill, New York, 1921.
153. Goldman, L. and R. R. McNary. *Acquired Hypersensitivity to the Chlorinated Ethylamine Vesicants.* Arch. Dermat. Syph. N. Y., **48**, 15–16 (1943).
154. Goldschlag, S. *Experiments on the improvement of the treatment of mustard gas lesions of the skin.* Med. J. Australia, 1942, **1**, 620–622.
155. T. Lewis and R. T. Grant. *Vascular Reactions of the Skin to Injury. Part II. The Liberation of a Histamine-like Substance in Injured Skin; The Underlying Cause of Factitious Urticaria and of Wheals Produced by Burning; and Observations Upon the Nervous Control of Certain Skin Reactions.* Heart, **11**, 209–265 (1924).
156. E. F. Lewison. *Sensitivity to War Gases.* (Letter to editor), J.A.M.A., **118**, 248 (1942).
157. E. K. Marshall, Jr., Vernon Lynch and Homer W. Smith. *On Dichlorethylsulphide (Mustard Gas). II.*

Variations in Susceptibility of the Skin to Dichlorethylsulphide. J. Pharmacol. Exp. Therap., **12**, 291-301 (1918).

158. V. Menkin. *Dynamics of Inflammation*. New York: Macmillan Company, 1940.
159. V. Menkin. *The significance of biochemical units in inflammatory exudates*. Science, **101**, 422-423 (1945).
160. I. A. Mirsky and L. Goldman, *The Production of Bullae in the Skin of the Duck*, Arch. Dermat. Syph., **48**, 161-163 (1943).
161. R. A. Peters. *Effect of Dichlorodiethyl-sulphone on Brain Respiration*. Nature, **138**, 327-328 (1936).
162. S. Rothman and P. Flesch. *The Physiology of the Skin*. Ann. Rev. Physiol., **6**, 195-224.
163. Charles Sheard. *Temperature of Skin and Thermal Regulation of the Body*. Pages 1523-1535 in Medical Physics, Otto Glasser, editor. The Year Book Publishers, Chicago, 1944.
164. Homer W. Smith, George H. A. Clowes and E. K. Marshall, Jr. *On Dichlorethylsulfide (Mustard Gas). IV. The Mechanism of Absorption by the Skin*. J. Pharmacol. Exp. Therap., **13**, 1-30 (1919).
165. Torald Sollmann. *Dichlorethylsulphid (Mustard Gas). I. The Influence of Solvents, Adsorbents and Chemical Antidotes on the Severity of the Human Skin Lesions*. J. Pharmacol. Exp. Therap., **12**, 303-318 (1918).
166. T. Sollmann. *Dichlorethylsulphid (Mustard Gas). II. The Question of Induced Hypersusceptibility of the Skin*, J. Pharmacol. and Exper. Ther., **12**, 319-321 (1919).
167. Edward Bright Vedder, *The Medical Aspects of Chemical Warfare*, 327, Williams and Wilkins, Baltimore, 1925.

Chapter 21

OSRD FORMAL REPORTS

1. OSRD 794. *The Relative Effectiveness of Chloramides Against Certain Toxic Agents*, by Homer Adkins, University of Wisconsin, August 3, 1942. Div. 9-541.22-M2
2. OSRD 1010. *Comparison of Impregnites Against Mustard*, by Homer Adkins, University of Wisconsin, November 14, 1942. Div. 9-541.22-M4
3. OSRD 1057. *The Preparation of S-461 from Methyl Ethyl Ketone*, by Homer Adkins, University of Wisconsin, November 30, 1942. Div. 9-511.3-M1
4. OSRD 1118. *A Summary of Research and Development Work in Connection with the Preparation and Use of S-461 as a Protective Agent Against Mustard*, by Homer Adkins, University of Wisconsin, December 9, 1942. Div. 9-511.3-M2
5. OSRD 1283. *Determination of the Thermal Stability of Chloramides and of Powders, Creams, and Ointments Containing them*, by Homer Adkins, University of Wisconsin, March 22, 1943. Div. 9-511-M2
6. OSRD 1289. *Reactions of 1070 and 1430 with Chloramides*, by Homer Adkins, University of Wisconsin, March 23, 1943. Div. 9-522.21-M2
7. OSRD 1760. *Products of the Decontamination of Mustard by Cloth Impregnated with S-461*, by Homer Adkins, University of Wisconsin, September 1, 1943. Div. 9-541.22-M5
8. OSRD 1762. *Comparison of Chloramides as Impregnants Against 1430*, by Homer Adkins, University of Wisconsin, September 1, 1943. Div. 9-541.22-M6
9. OSRD 3249. *Preparation and Testing of Substances as Neutralizing or Therapeutic Agents for H Burns*, by K. Folkers, R. F. Phillips, C. H. Shunk, H. Molitor, and S. Kuna, Merck and Company, February 15, 1944. Div. 9-522.12-M13
10. OSRD 3336. *The Laboratory and Semi-plant Preparation of S-461*, by J. Martin, The Commercial Solvents Corporation, March 25, 1944. Div. 9-511.3-M1
11. OSRD 3338. *The Preparation of Dimethylglycoluril*, by W. A. Fisher and W. Minnis, Allied Chemical and Dye Corporation, March 14, 1944. Div. 9-541.21-M1
12. OSRD 3386. *Tests of Chloramide-containing Ointments for Protection and Decontamination of Human Skin Against Vesicants*, by J. Savit, J. F. Thomson, E. Goldswasser, P. DeBruyn, M. A. Bloom, University of Chicago Toxicity Laboratory, March 21, 1944. Div. 9-511-M2
13. OSRD 3821. *Non-irritant Protective Ointments*, by P. L. Salzberg, W. A. Lazier, and W. J. Peppel, Chemical Department, E. I. duPont de Nemours and Company, July 1, 1944. Div. 9-510-M1
14. OSRD 4001. *Experimental Production of Dicetyl and Dimethylglycoluril*, by W. J. Hund, Shell Development Company, September 15, 1944. Div. 9-231.2-M3
15. OSRD 4216. *The Laboratory Preparation of S-428*, by J. Martin, Commercial Solvents Corporation, October 6, 1944. Div. 9-511.1-M1
16. OSRD 4305. *The Preparation of S-461 from Methyl Ethyl Ketone*, by Homer Adkins, J. E. Carnahan, and A. L. Wilds, University of Wisconsin, November 2, 1944. Div. 9-511.3-M5
17. OSRD 4591. *The Preparation of S-330 and Related Compounds*, by Homer Adkins, J. E. Carnahan, J. E. Castle, D. C. England, R. H. Gillespie, E. E. Royals, H. P. Schultz, and A. L. Wilds, University of Wisconsin, January 10, 1945. Div. 9-511.3-M2
18. OSRD 5384. *The Preparation of S-430 and Other Chloramides*, by Homer Adkins, J. E. Castle, J. E. Carnahan, D. England, R. H. Gillespie, Willa I. Guss, E. E. Royals, H. P. Schultz, and A. L. Wilds, University of Wisconsin, May 5, 1945. Div. 9-541.21-M2
19. OSRD 5429. *Permeable Protective Fabrics XLVII — S-461 Powder — Control of Thermal Propagation*, by Chemical Department, E. I. duPont de Nemours and Company, August 9, 1945. Div. 9-541.21-M3
20. OSRD 5554. *Permeable Protective Fabrics LV — Investigation of New Chloramides*, by Chemical Department, E. I. duPont de Nemours and Company, September 7, 1945. Div. 9-541.22-M9
21. OSRD 5555. *Permeable Protective Fabrics LVI — Evaluation of New Impregnites*, by Chemical Department, E. I. duPont de Nemours and Company, September 10, 1945. Div. 9-541-M1
22. OSRD 6084. *The NDRC Method for Laboratory Evaluation of Permeable Protective Fabrics Against Mustard*, by Willa I. Guss and Homer Adkins, University of Wisconsin, October 17, 1945. Div. 9-533.2-M2
23. OSRD 6109. *The Preparation of S-430*, by L. P. Kyrides,

O. J. Weinkauff, F. C. Meyer, and G. W. Ashworth, Monsanto Chemical Company, October 16, 1945. Div. 9-511.2-M3

24. OSRD 6111. *Preparation of the Chloroamides, S-361, S-328, S-330, S-430, S-233, S-300, S-221, S-436, and Decontaminant 40*, by R. T. Major, W. H. Engels, J. R. Stevens, M. Tishler, W. Bartholomew, W. A. Bittenbender, S. W. Brigge, E. R. Braun, P. Chemicz, W. S. Clewell, P. G. Colin, H. W. Ober, T. J. Webb, and F. J. Wolf, Merck and Company, October 17, 1945. Div. 9-511.4-M3
25. OSRD 6323. *Preparation of Various Types of Amides and Amidines and an Investigation of the Chlorinated Derivatives Thereof*, by D. W. Kaiser, American Cyanamid Company, November 15, 1945. Div. 9-229-M3
26. OSRD 6378. *Permeable Protective Fabrics LXX*, by Chemical Department, E. I. duPont de Nemours and Company, December 20, 1945. Div. 9-540-M2
27. OSRD 6390. *The Preparation of Isocyanates, Cyanuric Acid, and Decontaminant 40*, by R. L. Jenkins and E. E. Hardy, Monsanto Chemical Company, December 31, 1945. Div. 9-223.3-M3

UNITED STATES ARMY REPORTS

Chemical Warfare Service

28. EACD 392. *Protective Clothing*, January 2, 1927.
29. EATR 379. *A History of the Development of Protective Ointments*, January 13, 1943.
30. TDMR 420. *Summary of Data on Soluble and Insoluble Impurities in CC No. 2 (DPI and TCA)*, September 1, 1942.
31. TDMR 758. *A Survey of the Literature on Impregnites*, November 1, 1943.
32. *Impregnites: A Review*, report prepared by C. H. Greenewalt and submitted to Col. W. C. Kubrich, September 3, 1942.
33. *Report on Tests of Protective Clothing, Phase Three: Tropical Zone Tests*, Conducted Jointly by the Chemical Warfare Service, the Quartermaster Corps, and the Office of the Surgeon General. Part 1 — *Protective Value, Life Span and Physiological Effects of Impregnated Cotton Clothing in Tropic Zone — Final Report*, June 15, 1943; Part 2 — *Report on Observations of Tests of Protective Clothing* (undated); Part 3 — *Impregnated Cotton Clothing — A Physiological Field Study of Clothing Treated for Protection against Mustard-Type Irritants Worn by Soldiers in a Tropical Region (Panama)*, June 10, 1943. Edgewood Technical Library File, ETF 613.3-23.
34. Intelligence Division Report No. 3997. I. G. Farbenindustrie A.G., Hochst Am Main, Germany. Wehrmacht Items, July 7, 1945.

UNITED STATES NAVY REPORTS

Naval Research Laboratory

35. P-1807. *Investigation of Chloroamides for Use on Protective Clothing*, April 27, 1942.
36. P-2000. *Progress Report on Protective Clothing*, February 20, 1943.
37. P-2300. *A Study of S-330 as an Impregnite for Permeable Protective Clothing*, June 5, 1944.

BRITISH REPORTS

38. C.283-C-280. *Notes on a Meeting of the Vesicant Defence Section of the Gas Protection Subcommittee, Held Jointly with the Respirator Section at Porton on April 13, 1942.*

Chapter 25

OSRD FORMAL REPORTS

1. OSRD 1283. *Determination of the Thermal Stability of Chloroamides and of Powders, Creams, and Ointments Containing Them*, by Homer Adkins, University of Wisconsin, March 22, 1943. Div. 9-511-M2
2. OSRD 3249. *Preparation and Testing of Substances as Neutralizing or Therapeutic Agents for H Burns*, by Karl Folkers, R. F. Phillips, C. H. Shunk, Hans Molitor, and Samuel Kuna, Merck and Company, February 15, 1944. Div. 9-522.12-M13
3. OSRD 3386. *Tests of Chloroamide-Containing Ointments for Protection and Decontamination of Human Skin against Vesicants*, by J. Savit, J. F. Thomson, E. Goldwasser, P. DeBruyn, and M. A. Bloom, University of Chicago Toxicity Laboratory, March 21, 1944. Div. 9-511-M2
4. OSRD 3437. *A. Investigation of Detoxicants or Decontaminants for Mustard Gas. B. Enzyme Studies and Other Chemical Studies Bearing upon the Action of Certain Vesicants*, by Leslie Hellerman, Johns Hopkins University, April 4, 1944. Div. 9-522.12-M17
5. OSRD 3921. *Non-irritant Protective Ointments*, by P. L. Salzberg, W. A. Lazier, and W. J. Peppel, Chemical Department, E. I. du Pont de Nemours and Company, July 1, 1944. Div. 9-510-M1
6. OSRD 4372. *Protective and Therapeutic Agents for War Gases — Pigmented Protective Ointments*, by P. L. Salzberg, W. A. Lazier, and W. J. Peppel, Chemical Department, E. I. du Pont de Nemours and Company, November 22, 1944. Div. 9-511.2-M1
7. OSRD 4419. *The Preparation, Stability, and Irritancy of Protective Ointments*, by Homer Adkins, E. E. Royals, and A. L. Wilds, University of Wisconsin, December 2, 1944. Div. 9-511.4-M1
8. OSRD 4638. *Tests for Decontamination of Mustard and Nitrogen Mustards on Human Skin*, by E. Goldwasser, P. DeBruyn, J. F. Thomson, and J. Savit, University of Chicago Toxicity Laboratory, December 12, 1944. Div. 9-522-M3
9. OSRD 4768. *Development of Protective Ointments*, by W. H. Hartung and W. E. Weaver, University of Maryland, March 3, 1945. Div. 9-511.4-M2

MISCELLANEOUS

10. Letter to Brig. Gen. W. C. Kubrich (Chief, Technical Division, CWS) on ointments A and B, by C. S. Barwell, E. W. Goodpasture, and J. G. Hopkins, February 5, 1943. Div. 9-515-M2

UNITED STATES ARMY REPORTS

Chemical Warfare Service

11. EATR 379. *A History of the Development of Protective Ointments*, January 13, 1943.
12. MD(EA) 80. *An Evaluation of the Irritant, Protective, and Decontaminating Properties of S-461 Ointment*, May 20, 1943.
13. TDMR 506. *A Memorandum Report. Tests Conducted at Gadsden, Alabama, on Three Protective Ointments*, December 14, 1942.
14. TDMR 630. *Protective Ointments Prepared and Tested at Edgewood Arsenal, Md. from July 27, 1938 to January 10, 1941*, May 13, 1943.
15. TRLR 7. *An Evaluation of the Irritant, Protective, and Decontaminating Properties of M4 Ointment*, October 11, 1943.
16. TRLR 11. *An Evaluation of the Comparative Irritancy of Ointments M4 and S-461*, November 11, 1943.
17. TRLR 17. *An Evaluation of the Protective Properties of S-461 Ointments*, December 20, 1943.
18. TRLR 29. *An Evaluation of the Protective Properties of S-330 Ointment*, April 27, 1944.
19. TRLR 32. *An Evaluation of the Physiological Effects of Permeable Protective Clothing and Protective Ointment M5 in the Panama Area*, May 17, 1944.
20. TRLR 34. *An Evaluation of the Irritant and Decontaminant Properties of S-330 and S-461 Ointments*, May 31, 1944.
21. TRLR 42. *An Evaluation of the Irritant and Protective Properties of Ointments S-461, S-330, and S-145*, September 4, 1944.

UNITED STATES NAVY REPORTS

Naval Research Laboratory

22. P-1898. *Prophylaxis and Treatment of Burns Caused by Chemical Warfare Agents. (1) Treatment of Mustard Burns with S-461 Ointment in a Series of Controlled Experiments on Human Subjects*, April 24, 1942.
23. P-1899. *Prophylaxis and Treatment of Burns Caused by Chemical Warfare Agents. (2) Prophylaxis, as Applied to Prevention of Burns by Liquid Mustard with S-461 Ointment*, May 26, 1942.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

24. Porton Report No. 2229. *Improved Anti-Gas Ointments for Use under All Temperature Conditions. Vanishing Creams Containing Anti-gas*, August 21, 1941.
25. Porton Report No. 2310. *The Development of an Anti-gas Ointment Suitable for Use under All Temperature Conditions between 10° C and 50° C*, November 27, 1941.
26. Porton Report No. 2628. *The Toxicity of Impregnated Clothing (AV, CC2, and Impregnite B) and of Ointment Anti-gas No. 5*, June 20, 1944.
27. Porton Report No. 2631. *New Active Constituents for Anti-gas Ointments, Part I*, July 20, 1944.
28. Porton Report No. 2638. *Anti-gas Ointments for Use in the Tropics, Part I. Exploratory Experiments*, August 14, 1944.
29. Porton Departmental Report 133. *Anti-Gas Ointments*, December 15, 1939.

CANADIAN REPORTS

Chemical Warfare Laboratories, Ottawa

30. Chemical Warfare Laboratories Report No. 10. *S-461 Cream*, April 10, 1943.
31. Physiological Section Report No. 49. *Properties and Performance of S-330 Anti-gas Ointment Containing Dimethyl Phthalate*, March 8, 1945.

Division of Entomology, Dominion of Agriculture

32. C.P. 77. *Field Tests of the Repellent Value against Mosquitoes of Anti-gas Ointments When Used Alone and in Combination with Standard Biting Fly Repellents*, January 1945.

AUSTRALIAN REPORTS

33. CD (Australia) Report No. 14. *The Comparative Irritancies and Prophylactic Values of Ointments A.G. No. 6 and Ointment S-461 under Tropical Conditions*, January 22, 1944.
34. CD (Australia) Report No. 33. *Trials with American Ointment M6*, May 1, 1944.
35. CD (Australia) Report No. 73. *The Use of A.G Ointment No. 6 and American Ointment, Protective M5, to Attain Prophylaxis against Mustard Gas Vapour under Tropical Conditions*, May 4, 1945.
36. CD (Australia) Note No. 17. *Comparative Irritancy Trial of Anti-gas Ointments Containing S-461 and S-330*, April 4, 1944
37. CD (Australia) Note No. 45. *The Prophylactic Value of Anti-gas Ointments against Liquid Vesicant Contamination*, May 15, 1945

INDIAN REPORTS

38. CDRE (India) Report No. 284. *The Comparative Toxicity, Irritancy, and Anti-gas Values of Ointment, Anti-gas, No. 3A, and American Protective Ointment M5 under Tropical Conditions in India*, October 10, 1944.
39. CDRE (India) Report No. 291. *The Comparative Physiological Values of Ointments, No. 6, 3A, and American Protective Ointment M5 under Tropical Conditions in India*, April 11, 1945.

Chapter 26

OSRD FORMAL REPORTS

1. OSRD 638. *Stabilization of Impregnated Fabrics*, by Chemical Department, E. I. du Pont de Nemours and Company, June 22, 1942. Div. 9-541.22-M1
2. OSRD 3151. *Permeable Protective Fabrics, Thermal Decomposition of CC-2*, by Chemical Department, E. I. du Pont de Nemours and Company, January 13, 1944. Div. 9-541.1-M1

3. OSRD 3382. *Permeable Protective Fabrics V — Field Method of Impregnation with CC-2 and S-481 — Status Following Field Trials*, by Chemical Department, E. I. du Pont de Nemours and Company, March 15, 1944. Div. 9-542-M1

4. OSRD 3389. *Permeable Protective Fabrics VI — Development of Standard CC-2 Field Impregnation System*, by Chemical Department, E. I. du Pont de Nemours and Company, March 23, 1944. Div. 9-542-M2

5. OSRD 3988. *Permeable Protective Fabrics VIII — Survey of Aqueous Emulsifying-Dispersing Agents*, by Chemical Department, E. I. du Pont de Nemours and Company, August 1, 1944. Div 9-541.111-M1

6. OSRD 3998. *Permeable Protective Fabrics X — Methylcellulose as the Emulsifying-Dispersing Agent for the T of O Process of Impregnation*, by Chemical Department, E. I. du Pont de Nemours and Company, August 9, 1944. Div. 9-541.111-M2

7. OSRD 4002. *Permeable Protective Fabrics XI — Storage Tests on the Field Impregnating Set M-1*, by Chemical Department, E. I. du Pont de Nemours and Company, August 10, 1944. Div. 9-542.1-M1

8. OSRD 4427. *Permeable Protective Fabrics XIII — Development of Preground, Dry CC-2*, by Chemical Department, E. I. du Pont de Nemours and Company, December 4, 1944. Div. 9-541.1-M2

9. OSRD 4583. *Permeable Protective Fabrics XIV — Stabilization of CC-2 Impregnated Fabrics — Search for Agents Alternative to Zinc Oxide*, by Chemical Department, E. I. du Pont de Nemours and Company, January 15, 1945. Div. 9-541.113-M1

10. OSRD 4592. *Permeable Protective Fabrics XVI — Development of Evaluation Tests — Aging Properties*, by Chemical Department, E. I. du Pont de Nemours and Company, January 17, 1945. Div. 9-541.22-M7

11. OSRD 4599. *Permeable Protective Fabrics XVII — Effect of Fabric on Aging Stability - QM Series*, by Chemical Department, E. I. du Pont de Nemours and Company, January 18, 1945. Div. 9-541.112-M1

12. OSRD 4603. *Permeable Protective Fabrics XVIII — Effect of Fabric on Aging Stability of Impregnated Fabrics — 2nd QM Series Repo* , by Chemical Department, E. I. du Pont de Nemours and Company, January 19, 1945. Div. 9-541.112-M2

13. OSRD 4610. *Permeable Protective Fabrics XIX - Simplified Field Impregnation Systems CC-2, Exploratory Studies*, by Chemical Department, E. I. du Pont de Nemours and Company, January 20, 1945. Div. 9-542-M3

14. OSRD 4618. *Permeable Protective Fabrics XX — CC-2, Stability Tests on Clothing in Panama Troop Wearing Trial*, by Chemical Department E. I. du Pont de Nemours and Company, January 2, 1945. Div. 9-541.113-M2

15. OSRD 4759. *Permeable Protective Fabrics XXVII - Camouflage Pigmentation*, by Chemical Department, E. I. du Pont de Nemours and Company, March 1, 1945. Div. 9-541.111-M3

16. OSRD 4910. *Permeable Protective Fabrics XXXII Substitutes for Chloroparaffin*, by Chemical Department, E. I. du Pont de Nemours and Company, April 7, 1945. Div. 9-541.111-M4

17. OSRD 4922. *Permeable Protective Fabrics XXXIII — Substitutes for Chloroparaffin II*, by Chemical Department, E. I. du Pont de Nemours and Company, April 10, 1945. Div. 9-541.111-M4

18. OSRD 4936. *Permeable Protective Fabrics XXXIV — Stabilizers for CC-2*, by Chemical Department, E. I. du Pont de Nemours and Company, April 13, 1945. Div. 9-541.113-M3

19. OSRD 4941. *Permeable Protective Fabrics XXXV — Reimpregnation Studies*, by Chemical Department, E. I. du Pont de Nemours and Company, April 14, 1945. Div. 9-541.111-M6

20. OSRD 5072. *Permeable Protective Fabrics XXXVII — Reimpregnation Studies II*, by Chemical Department, E. I. du Pont de Nemours and Company, May 18, 1945. Div. 9-541.111-M6

21. OSRD 5081. *Permeable Protective Fabrics XXXVI — Washfastness of CC-2 Impregnated from Aqueous Dispersions*, by Chemical Department, E. I. du Pont de Nemours and Company, May 17, 1945. Div. 9-541.111-M7

22. OSRD 5421. *Permeable Protective Fabrics XLV - Stabilization and Evaluation of S-481-impregnated Fabrics*, by Chemical Department, E. I. du Pont de Nemours and Company, August 8, 1945. Div. 9-541.22-M8

23. OSRD 5427. *Permeable Protective Fabrics XLVI — Survey of Aqueous Emulsifying-Dispersing Agents*, by Chemical Department, E. I. du Pont de Nemours and Company, August 9, 1945. Div. 9-541.111-M8

24. OSRD 5431. *Permeable Protective Fabrics XLVIII — CC-2, S-481-Fabric Stabilization — Effect of Pretreatment on Stability of Impregnated Fabrics*, by Chemical Department, E. I. du Pont de Nemours and Company, August 10, 1945. Div. 9-541.113-M4

25. OSRD 5526. *Permeable Protective Fabrics LIII — CC-2, S-481 — Emergency Impregnation Systems for Tropical Shorts Only*, by Chemical Department, E. I. du Pont de Nemours and Company, September 4, 1945. Div. 9-542-M4

26. OSRD 5534. *Permeable Protective Fabrics LIV - Investigation of New Chloramides*, by Chemical Department, E. I. du Pont de Nemours and Company, September 5, 1945. Div. 9-541.22-M8

27. OSRD 5554. *Permeable Protective Fabrics LV — Investigation of New Chloramides*, by Chemical Department, E. I. du Pont de Nemours and Company, September 7, 1945. Div. 9-541.22-M8

28. OSRD 5555. *Permeable Protective Fabrics LVI — Evaluation of New Impregnites*, by Chemical Department, E. I. du Pont de Nemours and Company, September 10, 1945. Div. 9-541-M1

29. OSRD 6068. *Permeable Protective Fabrics LVIII — Skin Irritation — 1944 Edgewood Arsenal Wearing Tests*, by Chemical Department, E. I. du Pont de Nemours and Company, October 10, 1945 Div. 9-541.13-M2

30. OSRD 6089. *Permeable Protective Fabrics LIX CC-2 Retention of Impregnated Fabric During Wear*, by Chemical Department, E. I. du Pont de Nemours and Company, October 17, 1945. Div. 9-541.113-M5

31. OSRD 6090. *Permeable Protective Fabrics LX Stabilization of Fabric with Calcium Carbonate*, by Chemical

Department, E. I. du Pont de Nemours and Company, October 18, 1945. Div. 9-541.113-M6

32. OSRD 6191. *Permeable Protective Fabrics LXI — Development of Helmet Impregnating Set*, by Chemical Department, E. I. du Pont de Nemours and Company, December 11, 1945. Div. 9-542.1-M2
33. OSRD 6194. *Permeable Protective Fabrics LXIV — CC-2 Retention of Impregnated Fabric During Wear*, by Chemical Department, E. I. du Pont de Nemours and Company, December 12, 1945. Div. 9-541.113-M7
34. OSRD 6195. *Permeable Protective Fabrics LXV — Second Quartermaster Series*, by Chemical Department, E. I. du Pont de Nemours and Company, December 14, 1945. Div. 9-541.113-M8
35. OSRD 6196. *Permeable Protective Fabrics LXVI —Storage of Preground, Dry CC-2*, by Chemical Department, E. I. du Pont de Nemours and Company, December 14, 1945. Div. 9-541.1-M3
36. OSRD 6197. *Permeable Protective Fabrics LXVII — Effect of Fabric on Aging Quality of Stabilized Impregnated Fabrics*, by Chemical Department, E. I. du Pont de Nemours and Company, December 17, 1945. Div. 9-541.112-M4
37. OSRD 6198. *Permeable Protective Fabrics LXVIII — Development of Light Weight Field Impregnating Sets*, by Chemical Department, E. I. du Pont de Nemours and Company, December 17, 1945. Div. 9-542.1-M3
38. OSRD 6199. *Permeable Protective Fabrics LXIX Field Impregnating Set, M-1 Storage Tests (Concluded)*, by Chemical Department, E. I. du Pont de Nemours and Company, December 17, 1945. Div. 9-542.1-M4
39. OSRD 6378. *Permeable Protective Fabrics LXX*, by Chemical Department, E. I. du Pont de Nemours and Company, December 20, 1945. Div. 9-540-M2

UNITED STATES ARMY REPORTS

War Department Manuals

40. TM3-270. *Clothing Impregnating Plant M-. (T of O)*, February 4, 1944.

Chemical Warfare Service

41. EATR 100. *Permeable Protective Clothing*, August 29, 1933.
42. MDEAOMR 105. *The Toxic Effects of Acetylene Tetrachloride on the Operating Personnel of the M-1 Impregnating Plant*, August 9, 1943.
43. TDMR 1095. *The Stability and Irritancy of Permeable Protective Clothing, and the Irritancy of Ointment, Protective, M5, in Tropical Wearing Trials (Southwest Pacific Area)*, October 16, 1945.

Office of the Quartermaster General

44. *An Appraisal of Chemical Warfare Permeable Protective Clothing with Recommendations*, September 20, 1943.

UNITED STATES NAVY REPORTS

Naval Research Laboratory

45. P-2055. *Aqueous Impregnating Systems of Chlorinated Paraffin and Impregnite S-15*, May 12, 1943.
46. P-2207. *A Study of Chlorinated Paraffin as the Binding Agent for Protective Clothing Impregnated by the Aqueous Process*, May 27, 1944.
47. P-2406. *Report on Wearing Trials of Protective Clothing at Camp Lejeune, N.C.*, November 13, 1944.

Marine Corps

48. Marine Corps Equipment Board Project 420, Marine Barracks, Quantico, Va., *Impregnation Set, Light Weight Simplified Field*, June 15, 1945.

AUSTRALIAN REPORTS

49. CD (Australia) Report No. 18. *The Toxicity of AV Impregnated Clothing — Part I*, January 31, 1944.
50. CD (Australia) Note No. 10. *The Use of Underclothing Worn with AV Impregnated Garments*, April 10, 1944.
51. CD (Australia) Report No. 32. *The Toxicity of AV Impregnated Clothing — Part II*, April 3, 1944.
52. CD (Australia) Report No. 36. *Wearing Trial of AV Impregnated Cotton Clothing*, May 1, 1944.

Chapter 27

OSRD FORMAL REPORTS

1. OSRD 4940. *The Impregnation of Fabrics with Activated Carbon*, by W. J. Thackston, S. N. Glarum, and R. O. Steele, Rohm and Haas Company, April 9, 1945. Div. 9-541.111-M5
2. OSRD 5419. *Development of Plant Procedure for Preparation of Carbon-Impregnated Fabrics*, by W. P. Hall, Joseph Bancroft and Sons Company, August 7, 1945. Div. 9-541.11-M3
3. OSRD 5834. *Development of Gas Protective Rayon Yarns and Fabrics*, by J. L. Costa and R. A. Morse, Manville-Jenckes Corporation (Woonsocket Rayon Division), September 26, 1945. Div. 9-541.11-M4
4. OSRD 6081. *The NDRC Method for Laboratory Evaluation of Permeable Protective Fabrics against Mustard*, by W. I. Gass and Homer Adkins, University of Wisconsin, October 17, 1945. Div. 9-543.2-M2
5. OSRD 6192. *Permeable Protective Fabrics LXII — Carbon Impregnations from Water Suspension*, by Chemical Department, E. I. du Pont de Nemours and Company, December 12, 1945. Div. 9-541.111-M9
6. OSRD 6193. *Permeable Protective Fabrics LXIII — Carbon Impregnations from Organic Solvent Suspension*, by Chemical Department, E. I. du Pont de Nemours and Company, December 12, 1945. Div. 9-541.11-M6
7. OSRD 6272. *Preparation of Carbon-Coated Protective Fabrics*, by Dana Burks, Jr. and R. H. Gillespie, Kendall Company, and G. E. Sinkinson and H. I. Huey, Sayles Finishing Plants, Incorporated, February 14, 1946. Div. 9-541.11-M7
8. OSRD 6287. *Rayon Containing Activated Carbon for Use in Protective Clothing*, by S. A. Moss, Jr., American Viscose Corporation, November 19, 1945. Div. 9-541.11-M5
9. OSRD 6412. *Correlation of Standard CWS Test Data with*

NDRC Titrimeter Data, by L. C. Hurd, O. B. Hager, E. M. Young, and D. B. Reisner, Rohm and Haas Company, December 21, 1945. Div. 9-543.2-M3

OSRD INFORMAL REPORT

10. Contract OEMsr-635, Sayles Finishing Company, G. E. Sinkinson, *Informal Report with Regard to Estimated Cost of Carbon-Coated Fabrics*, November 2, 1944. Div. 9-541.11-M1

MISCELLANEOUS

11. Division 10 Summary Technical Report, Chapter 3. *The Manufacture of Activated Charcoal*, W. L. McCabe.
12. OEMsr-1327, American Viscose Corporation, R. Bouvet, Correspondence, August 4, 1944. Div. 9-713-M1

UNITED STATES ARMY REPORTS

Chemical Warfare Service

13. MIT-MR No. 71. *Field Impregnation of Cotton Garments with Charcoal Fines*, May 10, 1944.
14. MIT-MR No. 184. *Emergency Field Impregnation of Clothing with Charcoal Fines*, September 19, 1945
15. TCIR 183. *Preliminary Evaluation of Experimental Carbon Fabrics*, September 1, 1944.
16. TCIR 247. *Preliminary Evaluation of Experimental Carbon Fabrics, Part II*, February 12, 1945.
17. TDMR 930. *The H-Vapor Protection Afforded by One and One-Half Layer Protective Outfits Worn by the Same Men in Successive Exposures, Gas Chamber Tests — Part I*, March 1, 1945.
18. TDMR 1014. *A Study of the Effect of Mill Processing on the Stability, after Protective Impregnation, of Forty-Two Herringbone Twill Fabrics, Based on Data Obtained by Four Agencies*, May 14, 1945.

MISCELLANEOUS

19. QM Specification 6-261, January 7, 1939, and Amendment No. 1, May 24, 1940.
20. Technical Study No. 63. *Cloth Impregnated with Charcoal Fines*, May 15, 1942.

UNITED STATES NAVY REPORTS

Naval Research Laboratory

21. P-2322. *The Evaluation of Activated Carbon as an Anti-Vesicant Agent in Protective Clothing*, July 3, 1944.
22. P-2655. *Evaluation of Carbon-Rayon Protective Fabrics*, December 20, 1945.
23. P-2682. *2nd Wearing Trial of Protective Clothing at Camp Lejeune, North Carolina*, November 26, 1945.
24. P-2701. *Chamber Tests with Human Subjects XIV — Tests of New Carbon Clothing*, December 3, 1945.
25. P-2702. *Chamber Tests with Human Subjects XV — Tests of Worn Carbon Clothing*, January 16, 1946.
26. P-2703. *Chamber Tests with Human Subjects XVI — Tests of Regenerated and Decontaminated Carbon Clothing*, to be issued in 1946.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

27. Porton Report No. 2354. *The Protective Value of Carbon-Impregnated Fabrics against H Vapour*, May 20, 1942.
28. Porton Report No. 2374. *The Protection of Vulnerable Areas of the Body against H Vapour in Hot Climates*, May 22, 1942.
29. Ptn. 2400 (U.9807). *Carbon-Impregnated Clothing*, June 3, 1944.

Extramural Research

30. University College, Southampton (N. K. Adam)
a. W.232. *Penetration of CW Agents*, by N. K. Adam, A. Lawson, and K. B. Webb, April 7, 1942.
31. Imperial College, London (J. H. De Boer)
a. W.19320A. *Selective Adsorption of Mustard Gas from Different Solvents on Sulphides and Other Compounds*, by J. H. De Boer and E. D. G. Fraim, (received by NDRC, March 25, 1943).

MISCELLANEOUS

32. V.3907, *Sixth Interim Report on Charcoal Impregnated Cloths*, Wool Industries Research Association, April, 1941.
33. W.3338 *Ad Hoc Meeting to Discuss the Progress of Research on the Carbon Impregnation of Clothing, Held at Porton on May 20, 1942*, June 27, 1942.

OPEN LITERATURE

Improved Instrument for Measuring the Air Permeability of Fabrics

34. Schiefer, H. F. and P. M. Boyland, *Journal of Research of National Bureau of Standards*, **28**, 637 (1942).

MISCELLANEOUS

35. Unpublished work carried out under the supervision of Mr. Henry R. Childs of the Tennessee Eastman Corporation, Acetate-Rayon Division, Kingsport, Tennessee (1943).
36. Unpublished work carried out under the supervision of Dr. E. W. Rugeley of the Carbide and Carbon Chemicals Corporation, Research and Development Department, South Charleston, West Virginia (1943).

Chapter 28

OSRD FORMAL REPORTS

1. OSRD 4880. *A Study of the Decontamination of Surfaces Which Have Been Exposed to Chemical Warfare Agents — Special Study of the Decontamination and Regeneration of Carbon Fabrics*, by J. E. Kirby, H. S. Rothrock, C. T. Handy, and R. N. MacDonald, Chemical Department, E. I. du Pont de Nemours and Company, April 2, 1945. Div. 9-541.112-M3
2. OSRD 5502. *Studies of Carbon-Coated and Carbon-Impreg-*

nated Fabrics – Laundering Procedures — Wearing Trials, by S. N. Gharm and R. O. Steele, Rohm & Haas Company, August 28, 1945. Div. 9-541.112-M3

2. OSRD 6272. *Preparation of Carbon-Coated Protective Fabrics*, by Dana Burks, Jr. and R. H. Gillespie, Kendall Company, and G. E. Sinkinson and H. I. Huey, Sayles Finishing Plants, Inc., February 14, 1946. Div. 9-541.11-M7

UNITED STATES ARMY REPORTS

Chemical Warfare Service

4. MST-MR No. 84. *Miscellaneous Tests of Carbon Cloth*, June 23, 1944.
5. TDMR 1012. *The H-Vapor Protection Afforded by Various Protective Outfits Worn by the Same Men in Successive Exposures*, June 27, 1945.

UNITED STATES NAVY REPORTS

Naval Research Laboratory

6. P-2239. *Chamber Tests with Human Subjects IV — Tests of Carbon Clothing against H Vapor*, February 25, 1944.
7. P-2322. *The Evaluation of Activated Carbon as an Anti-Vesicant Agent in Protective Clothing*, July 3, 1944.
8. P-2570. *The Persistence of H and HN on Carbon Clothing*, July 12, 1945.
9. P-2604. *Chamber Tests with Human Subjects XIII — Special Tests of CC-2 and Carbon Protective Clothing*, August 18, 1945.
10. P-2655. *Evaluation of Carbon-Rayon Protective Fabrics*, December 20, 1945.
11. P-2682. *Second Wearing Trials of Protective Clothing at Camp Lejeune, North Carolina*, November 26, 1945.
12. P-2701. *Chamber Tests with Human Subjects XIV — Tests of New Carbon Clothing*, to be issued in 1946.
13. P-2702. *Chamber Tests with Human Subjects XV — Tests of Worn Carbon Clothing*, to be issued in 1946
14. P-2703. *Chamber Tests with Human Subjects XVI — Tests of Regenerated and Decontaminated Carbon Clothing*, to be issued in 1946.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

15. Porton Report No. 2264. *Detector Papers for Vesicants*, September 10, 1941.
16. Porton Report No. 2354. *The Protective Value of Carbon-Impregnated Fabrics against H Vapour*, May 20, 1942.
17. Porton Report No. 2390. *The Protective Value of Carbon-Impregnated Fabrics against H Vapour*, August 5, 1942.

Chapter 29

OSRD FORMAL REPORTS

1. OSRD 6084. *The NDRC Method for Laboratory Evaluation of Permeable Protective Fabrics against Mustard*, by Willa I. Guss and Homer Adkins, University of Wisconsin, October 17, 1945. Div. 9-543.2-M2
2. OSRD 6272. *Preparation of Carbon-coated Protective Fabrics*, by Dana Burks, Jr. and R. H. Gillespie, The Kendall Company, and G. E. Sinkinson and H. I. Huey, Sayleaville Finishing Plants, Inc., November 1, 1945. Div. 9-541.11-M7
3. OSRD 6347. *Test Methods Used for the Evaluation of Protective Fabrics against Vesicant Gases at the Rohm and Haas Laboratories*, by L. C. Hurd, O. B. Hager, E. M. Young, and R. W. Brown, Rohm and Haas Company, January 4, 1946. Div. 9-543.2-M4

UNITED STATES ARMY REPORTS

Chemical Warfare Service

4. PCS Report No. 9. *Résumé of Recent Knowledge on the Technical Aspects of Chemical Warfare in the Field*, May 17, 1945.
5. CWS Directive No. 162. *Mustard Vapor Resistance Test on Permeable Materials*, July 11, 1942.

UNITED STATES NAVY REPORTS

Naval Research Laboratory

6. P-1831. *Method of Determination of the Penetration of HS Vapor through Protective Clothing*, January 6, 1942.
7. P-2720. *Chemical Evaluation of the Leakage of H Vapor through Protective Clothing*, 1946.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

8. Porton Report No. 2264. *Detector Papers for Vesicants*, September 10, 1941.
9. Porton Report No. 2294 (Addendum). *Use of No. 2 Detector Paper (S.D.) in Detection of H in Soils*, January 28, 1942.

Chapter 30

OSRD FORMAL REPORTS

1. OSRD 4618. *Permeable Protective Fabrics XX — CC-2 — Stability Tests on Clothing in Panama Troop Wearing Trial*, by Chemical Department, E. I. du Pont de Nemours and Company, January 22, 1945. Div. 9-541.113-M2
2. OSRD 4624. *Permeable Protective Fabrics XXI – Skin Irritation*, by Chemical Department, E. I. du Pont de Nemours and Company, January 23, 1945. Div. 9-541.13-M1
3. OSRD 6008. *Permeable Protective Fabrics LVIII — Skin Irritation — 1944 Edgewood Arsenal Wearing Tests*, by Chemical Department, E. I. du Pont de Nemours and Company, October 10, 1945. Div. 9-541.13-M2
4. OSRD 6084. *The NDRC Method for Laboratory Evaluation of Permeable Protective Fabrics against Mustard*, by W. I. Guss and Homer Adkins, University of Wisconsin, October 17, 1945. Div. 9-543.2-M2

5. OSRD 6102. *Permeable Protective Fabrics LXII — Carbon Impregnations from Water Suspension*, by Chemical Department, E. I. du Pont de Nemours and Company, December 12, 1945. Div. 9-541.111-M9
6. OSRD 6104. *Permeable Protective Fabrics LXIV — CC-2 Retention of Impregnated Fabric During Wear*, by Chemical Department, E. I. du Pont de Nemours and Company, December 12, 1945. Div. 9-541.113-M7
7. OSRD 6105. *Permeable Protective Fabrics LXV — Second Quartermaster Series*, by Chemical Department, E. I. du Pont de Nemours and Company, December 14, 1945. Div. 9-541.113-M8
8. OSRD 6107. *Permeable Protective Fabrics LXVII — Effect of Fabric on Aging Quality of Stabilized Impregnated Fabrics*, by Chemical Department, E. I. du Pont de Nemours and Company, December 17, 1945. Div. 9-541.112-M4
9. OSRD 6272. *Preparation of Carbon-Coated Protective Fabrics*, by Dana Burks, Jr. and R. H. Gillespie, The Kendall Company, and G. E. Simkinson and H. I. Huey, Sayle Finishing Plants, Inc., February 14, 1946. Div. 9-541.11-M7
10. OSRD 6287. *Rayon Containing Activated Carbon for Use in Protective Clothing*, by S. A. Moss, Jr., American Viscose Corporation, November 19, 1945. Div. 9-541.11-M5
11. OSRD 6408. *Determination of (a) the Irritancy of Protective Ointments, (b) the Vesicant Properties of Contaminated Carbon Protective Fabrics, and (c) the Stability of CC-2 Impregnated Herringbone Twill Patches under Conditions of Semi-tropical Wear*, by H. O. Calvery, C. D. Johnston, W. Sherwood Lawrence, and E. J. Umberger, Federal Security Agency, March 8, 1946. Div. 9-500-M3

OSRD INFORMAL REPORTS

12. Contract NDCrc-132, University of Chicago Toxicity Laboratory, E. M. K. Geiling, Informal Monthly Progress Report, February 28, 1945. Div. 9-125-M2
13. Contract OEMsr-779, the Kendall Company, Dana Burks, Jr., Informal Monthly Progress Report, January 11, 1945. Div. 9-541.11-M2

UNITED STATES ARMY REPORTS

Chemical Warfare Service

14. SJPR 30. *Dropping Trial with M70 Bombs Charged Mustard Gas on Jungle Terrain*, October 15, 1944.
15. SJPR31. *Assessment of the 4.2 Inch M.L. Mortar Bomb, Charged HT, under Jungle Conditions*, May 14, 1945.
16. SJPR 34. *Assessment of Multiple Cluster Bombing with E20R1 Clusters of Canadian L.C. 50 Pound A C Bombs, Charged Levinstein H*, August 31, 1945.
17. SJPR 39. *Assessment of Multiple Cluster Bombing with E20R1 Clusters of Canadian 50 Pound L.C. Bombs Charged HT*, June 12, 1945.
18. SJPR 73. *Multiple Bombing Assessment of British Bombs, Aircraft, L.C. 500 Pound, Mark II, Fitted with T51 (BRTG 60) Fuzes and Charged HT, When Dropped from High Altitudes onto Jungle Terrain*, July 28, 1945.
19. SJPR 80. *H Spray Penetration of Jungle Canopy*, May 30, 1945.
20. SJPR 82. *The Effectiveness of Standard Anti-gas Training as Applied to Jungle Warfare, and the Effects Produced on Troops by Wearing Impregnated Clothing and Gas Masks in the Jungle (Kweiyu Sandfly)*, September 1, 1945.
21. TDMR 630. *Nitrogen Mustards, Comparative Vesicant Action and Cloth Penetration*, May 28, 1943.
22. TDMR 770. *Field Test to Determine the Tolerance of Men in Temperate Summer Climate to Water-Suspension-Impregnated Clothing*, March 1, 1944.
23. TDMR 845. *Vesicant Protection Afforded by Permeable Protective Clothing, Literature Survey of Information Available to 1 March, 1944*, August 21, 1944.
24. TDMR 913. *Tropical Jungle Wearing Tests of Six Types of Fatigue Garments Impregnated by Means of the Set, Field, Impregnated M-1*, January 15, 1945.
25. TDMR 930. *The H-Vapor Protection Afforded by One and One-Half Layer Protective Outfits Worn by the Same Men in Successive Exposures, Gas Chamber Tests — Part I*, March 1, 1945.
26. TDMR 970. *Investigation of the Physiological Effects, Protective Life Span, and Protection Afforded by Protective Clothing at Edgewood Arsenal*, February 8, 1945.
27. TDMR 1012. *The H-Vapor Protection Afforded by Various Protective Outfits Worn by the Same Men in Successive Exposures*, June 27, 1945.
28. TDMR 1042. *Protection Afforded by One and One-Half Layer Protective Outfits against Successive Exposures to H Vapor, Gas Chamber Tests — Part V*, May 22, 1945.
29. TDMR 1062. *Exposures of Permeable Protective Fabrics on Men's Arms to H Vapor. Preliminary Gas Chamber Tests*, August 21, 1945.
30. TDMR 1063. *Foam Impregnation of Clothing by the Water Suspension Process*, July 22, 1945.
31. TDMR 1095. *The Stability and Irritancy of Permeable Protective Clothing, and the Irritancy of Ointment, Protective M5, in Tropical Wearing Trials (Southwest Pacific Area)*, October 16, 1945.
32. TRLR 32. *An Evaluation of the Physiological Effects of Permeable Protective Clothing and Protective Ointment M5 in the Panama Area*, May 17, 1944.
33. TRLR 47. *Gassing Chamber for Human Tests; Construction and Operation*, October 25, 1944.
34. Dugway Proving Ground Report for Week Ending August 9, 1944. Part C - Dugway Proving Ground Mobile Field Unit Weekly Report (Bushnell), Series 2 — Report No. 68, for Week Ending July 29, 1944.
35. Dugway Proving Ground Report for Week Ending November 15, 1944. Part B - Medical Research Laboratory Weekly Report No. 33 (November 9-15, 1944).
36. Dugway Proving Ground Report for Week Ending February 13, 1945. Part B — Medical Research Laboratory Weekly Report No. 46 (February 7-13, 1945).
37. Dugway Proving Ground Report for Week Ending April 3, 1945. Part B - Medical Research Laboratory Weekly Report No. 53 (March 28-April 3, 1945).
38. Dugway Proving Ground Report for Week Ending May 22, 1945. Part B - Medical Research Laboratory Weekly Report No. 60 (May 16-22, 1945).

39. Medical Division Informal Monthly Progress Report for August 1945, August 15, 1945.

MISCELLANEOUS

40. TC 25. *Use, Care, and Preservation of Protective Clothing*, March 2, 1943.
41. *Report on Joint Test of Protective Clothing, Phase 2, Clothing Worn in Moderate Winter Climate*, conducted by the Quartermaster Board and the Chemical Warfare Service Technical Command, May 26, 1943.
42. *Report on Tests of Protective Clothing, Phase Three: Tropical Zone Tests*, conducted jointly by the Chemical Warfare Service, the Quartermaster Corps, and the Office of the Surgeon General. *Part 1 — Protective Value, Life Span and Physiological Effects of Impregnated Cotton Clothing in Tropic Zone — Final Report*, June 15, 1943; *Part 2 — Report on Observations of Tests of Protective Clothing* (undated); *Part 3 — Impregnated Cotton Clothing — A Physiological Field Study of Clothing Treated for Protection against Mustard-type Irritants Worn by Soldiers in a Tropical Region (Panama)*, June 10, 1943. Edgewood Technical Library File ETF 613.3-23.
43. Desert Warfare Board Report. *Carbon-coated Clothing*, November 24, 1943.
44. *Extracts from "Battle Experiences" as Put Out by General Bradley's Hqs. with Comments by A. St. John, Col., CWS*, July 29, 1944. Edgewood Technical Library File ETF 350-208.

UNITED STATES NAVY REPORTS

Naval Research Laboratory

45. P-2208. *Report on Chamber Tests with Human Subjects - I. Design and Operation of Chamber, II. Initial Tests of Navy Issue Protective Clothing against H Vapor*, December 22, 1943.
46. P-2219. *Chamber Tests with Human Subjects — III. Design, Operation and Calibration of a Chamber for Exposing Forearms to H Vapor*, January 22, 1944.
47. P-2230. *Chamber Tests with Human Subjects — IV. Tests of Carbon Clothing against H Vapor*, February 25, 1944.
48. P-2322. *The Evaluation of Activated Carbon as an Anti-vesicant Agent in Protective Clothing*, July 3, 1944.
49. P-2343. *Tropical Wearing Trials of Protective Clothing*, August 5, 1944.
50. P-2406. *Report on Wearing Trials of Protective Clothing at Camp Lejeune, North Carolina*, November 13, 1944.
51. P-2464. *Report on Chamber Tests with Human Subjects — V. Arm Chamber Exposures to HN Vapors*, March 1945.
52. P-2483. *Chamber Tests with Human Subjects — VI. Arm Chamber Exposures to L Vapor*, May 31, 1945.
53. P-2528. *Chamber Tests with Human Subjects — VII. The Effect of Concentration of H Vapor and Time of Exposure on the Protection Afforded by CC-2 Impregnated Clothing*, July 5, 1945.
54. P-2579. *Chamber Tests with Human Subjects — IX. Basic Tests with H Vapor*, August 14, 1945.
55. P-2580. *Chamber Tests with Human Subjects — X. Protection Afforded by CC-2 Impregnated Clothing under Various Conditions of Exposure*, September 7, 1945.
56. P-2597. *Chamber Tests with Human Subjects - VIII. Evaluation of Worn CC-2 Impregnated Clothing*, September 5, 1945.
57. P-2602. *Chamber Tests with Human Subjects — XI. Evaluation of Modified Aqueous CC-2 Impregnation Systems*, August 18, 1945.
58. P-2603. *Chamber Tests with Human Subjects — XII. Suit and Man "Breaks" with CC-2 Impregnated Clothing*, August 31, 1945.
59. P-2604. *Chamber Tests with Human Subjects — XIII. Special Tests of CC-2 and Carbon Protective Clothing*, August 18, 1945.
60. P-2655. *Evaluation of Carbon-rayon Protective Fabrics*, December 20, 1945.
61. P-2682. *Second Wearing Trial of Protective Clothing at Camp Lejeune, North Carolina*, November 26, 1945.
62. P-2688. *Chamber Tests with Human Subjects — XVII. Supplementary Tests of CC-2 Protective Clothing*, November 15, 1945.
63. P-2695. *A Summary of Wearing Trials of Permeable Protective Clothing*, November 26, 1945.
64. P-2701. *Chamber Tests with Human Subjects — XIV. Tests of New Carbon Clothing*, December 3, 1945.
65. P-2702. *Chamber Tests with Human Subjects — XV. Tests of Worn Carbon Clothing*, January 16, 1946.
66. P-2734. *Chamber Tests with Human Subjects — XVIII. Tests with HN Vapors*, January 14, 1946.
67. C-877-2(450-HWC). *Tests of Carbon Clothing against Vesicants*, September 26, 1944.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

68. Porton Report No. 2028. *The Toxicity of Impregnated Clothing (AV, CC2, and Impregnite B) and of Ointment Anti-gas No. 5*, June 20, 1944.

CANADIAN REPORTS

Experimental Station, Suffield, Alberta

69. Suffield Technical Minute No. 93. *Observations of the Skin Sensations Experienced during Exposure to CK*, April 20, 1945.

AUSTRALIAN REPORTS

70. CD (Australia) Report No. 18. *Toxicity of AV Impregnated Clothing*, January 31, 1944.
71. CD (Australia) Report No. 30. *An Attack on a Small Island with the M.47 Bomb Charged Levinstein Mustard, Final Report*, April 1, 1944.
72. CD (Australia) Report No. 34. *Comparative Wearing Trial of American Clothing Impregnated by the M1 and M2 Processes*, May 1, 1944.
73. CD (Australia) Report No. 38. *An Attack on a Small Island with the 65-lb. L.C. Bomb Charged Y3*, May 18, 1944.
74. CD (Australia) Report No. 41. *Effect of Varying Activity of Subjects during Exposure on the Sensitivity of Human Skin to Mustard Vapor*, May 19, 1944.

75. CD (Australia) Report No. 48. *Preliminary Wearing Trial of Australian Battle Dress Impregnated by the M1 and M2 Processes*, May 29, 1944.
76. CD (Australia) Report No. 60. *The Protective Life and Irritancy of New M2 Impregnated Clothing*, April 13, 1945.
77. CD (Australia) Report No 78. *A Further Comparison between Physiological Effects of Mustard Vapour in the Chamber and in the Field*, May 25, 1945.
78. CD (Australia) Note No. 35. *The Toxicity of A.V. Impregnated Clothing, Part III. Effects under Cooler Weather Conditions*, December 6, 1944.
79. CD (Australia) Note No. 41. *The Effect of High and Low Mustard Vapour Concentrations on the Dosage Required to Penetrate Impregnated Clothing*, May 16, 1945.

INDIAN REPORT

80. CDRE (India) Report No. 288. *The Toxicity and Irritancy of Impregnated Pervious Clothing under Tropical Conditions in India, Part IV. Wearing Trials with M1 (CC2) and M2 (XXCC3) Impregnated Garments*, January 25, 1945.

Chapter 31

OSRD FORMAL REPORTS

1. OSRD 1111. *Preparation of BAL*, by Chemical Department, E. I. du Pont de Nemours and Company, December 8, 1942. Div. 9-513.1-M1
2. OSRD 1221. *Experimental Manufacture and Process Study of BAL*, by Jackson Laboratory, E. I. du Pont de Nemours and Company, December 8, 1942. Div. 9-513.1-M2
3. OSRD 1370. *Water-soluble BAL Derivatives*, by M. S. Kharasch, University of Chicago, May 1, 1943. Div. 9-513.2-M1
4. OSRD 1652. *CMR-NDRC Joint Project on BAL Ointment. Report on the Work of the Pharmaceutical and Chemical Subcommittee for the Period January through April 1943*, by W. A. Lazier, E. I. du Pont de Nemours and Company, July 28, 1943. Div. 9-513.3-M1
5. OSRD 2056. *The Resolution of BAL*, by H. R. Snyder, University of Illinois, November 25, 1943. Div. 9-513.1-M3
6. OSRD 3249. *Preparation and Testing of Substances as Neutralizing or Therapeutic Agents for H Burns*, by Karl Folkers, R. F. Phillips, C. H. Shunk, Hans Molitor, and Samuel Kuna, Merck and Company, February 15, 1944. Div. 9-522.12-M13
7. OSRD 4460. *Protective and Therapeutic Agents for War Gases — Preparation of New Antidotes*, by P. L. Salzberg, W. A. Lazier, M. W. Farlow, and W. J. Peppel, E. I. du Pont de Nemours and Company, December 14, 1944. Div. 9-522.12-M19
8. OSRD 4604. *Protective and Therapeutic Agents for War Gases — BAL Derivatives and Analogs*, by P. L. Salzberg, W. A. Lazier, F. K. Signaigo, and A. A. Pavlic, E. I. du Pont de Nemours and Company, January 22, 1945. Div. 9-513.2-M2
9. OSRD 4988. *Protective and Therapeutic Agents for War Gases — Solutions of BAL*, by P. L. Salzberg, W. A. Lazier, G. W. Rigby, and C. G. Wortz, E. I. du Pont de Nemours and Company, April 2, 1945. Div. 9-513.3-M2
10. OSRD 5078. *Analogs and Derivatives of BAL*, by P. L. Salzberg, B. W. Howk, and W. H. Vinton, E. I. du Pont de Nemours and Company, January 15, 1946. Div. 9-513.2-M3
11. OSRD 5979. *Protective and Therapeutic Agents for War Gases: Therapeutic Agents for Mustard and Nitrogen Mustards II*, by P. L. Salzberg, W. A. Lazier, B. W. Howk, A. A. Pavlic, G. W. Rigby, and W. H. Vinton, E. I. du Pont de Nemours and Company, January 10, 1946. Div. 9-522-M4
12. OSRD 6428. *Protective and Therapeutic Agents for War Gases: Final Summary Report*, by P. L. Salzberg, B. W. Howk, W. A. Lazier, D. C. England, M. W. Farlow, C. M. Langkammerer, A. A. Pavlic, W. J. Peppel, G. W. Rigby, F. K. Signaigo, W. H. Vinton, J. H. Werntz, and C. G. Wortz, E. I. du Pont de Nemours and Company, January 15, 1946. Div. 9-515-M5

BRITISH REPORT

Research Establishment, Sutton Oak

13. S.O. R 611. *2,3-Dithiolpropanol (DTH). Part I. Preparation by the 2,3-dibromopropanol Method*, July 24, 1942.

Extramural Research

14. Cambridge University and Imperial College of Science and Technology (Malcolm Dixon). Z.1576 (Dixon Report No. 26). *BAL-Intrav: A New Non-toxic Thiol for Intravenous Injection in Arsenical Poisoning*, by J. F. Danielli, M. Danielli, P. D. Mitchell, L. N. Owen, and G. Shaw, April 21, 1944.
15. Oxford Biochemical Laboratory (R. A. Peters). V.2403-B (Report No. 33). *Treatment of Arsenical Burns with Dithiol Compounds*, by L. S. Stocken and R. H. Thompson, April 30, 1941.
16. V.9118 (Report No. 35). *DTH and Its Lewisite Derivative*, by L. A. Stocken and R. H. S. Thompson, August 8, 1941.
17. Report No. 30 (Research Item No. 21). *Preliminary Report on the Chemistry of Dithiol Compounds*, by L. A. Stocken and R. H. S. Thompson, March 7, 1941.

OPEN LITERATURE

18. Waters, L. L. and Stock, Chester. *BAL (British Anti-Lewisite)*. Science, **102**, 601 (1945).
19. Peters, R. A., Stocken, L. A., and Thompson, R. H. S. *British Anti-Lewisite (BAL)*, Nature, **156**, 616 (1945).

Chapter 32

OSRD FORMAL REPORTS

1. OSRD 794. *The Relative Effectiveness of Chloramnides against Certain Toxic Agents*, by Homer Adkins, University of Wisconsin, July 7, 1942 Div. 9-511.22-M2
2. OSRD 795. *The Action of Decontaminants on Mustard*

Gas, by C. S. Marvel and R. C. Fuson, University of Illinois, August 7, 1942. Div. 9-564-M3

3. OSRD 912. *The Solubilities of Impregnites in Various Solvents*, by Lee Irvin Smith, University of Minnesota, September 22, 1942. Div. 9-541.23-M1
4. OSRD 1010. *Comparison of Impregnites against Mustard*, by Homer Adkins, University of Wisconsin, November 14, 1942. Div. 9-541.22-M4
5. OSRD 1508. *The Chemistry of Chloro Sulfides and N-Chloro Compounds: Reactions Involved in the Decontamination of Mustard Gas*, by C. D. Hurd, Northwestern University, June 21, 1943. Div. 9-564-M4
6. OSRD 1760. *Products of the Decontamination of Mustard by Cloth Impregnated with S-501*, by Homer Adkins, University of Wisconsin, September 7, 1943. Div. 9-541.22-M5
7. OSRD 1762. *Comparison of Chloramides as Impregnants against H-9*, by Homer Adkins, University of Wisconsin, September 8, 1943. Div. 9-541.22-M6
8. OSRD 3131. *A Study of the Decontamination of Painted Surfaces Which Have Been Exposed to Chemical Warfare Agents — Special Assignment on Estimation of Extent of Damage Which Would Result from a War Gas Attack on Factories*, by J. E. Kirby, H. S. Rothrock, J. C. Sauer, R. N. MacDonald, and F. C. McGrew, Chemical Department, E. I. du Pont de Nemours and Company, January 22, 1944. Div. 9-562-M1
9. OSRD 3132. *A Study of the Decontamination of Painted Surfaces Which Have Been Exposed to Chemical Warfare Agents. Special Study of the Effect of HS and Decontamination Treatments on Airplane Fabrics*, by J. E. Kirby, H. S. Rothrock, and R. N. MacDonald, Chemical Department, E. I. du Pont de Nemours and Company, January 22, 1944. Div. 9-562-M2
10. OSRD 3133. *The Study of the Decontamination of Painted Surfaces Which Have Been Exposed to Chemical Warfare Agents*, by J. E. Kirby, H. S. Rothrock, R. N. MacDonald, F. C. McGrew, and J. C. Sauer, Chemical Department, E. I. du Pont de Nemours and Company, January 24, 1944. Div. 9-562-M3
11. OSRD 3437. *A. Investigation of Intoxicants or Decontaminants for Mustard Gas. B. Enzyme Studies and Other Chemical Studies Bearing upon the Action of Certain Vesicants*, by Leslie Hellerman, Johns Hopkins University Medical School, April 15, 1944. Div. 9-522.12-M17
12. OSRD 3501. *Tests for Decontamination of Lewisite on Human Skin*, by J. F. Thomson, Eugene Goldwasser, Joseph Savit, E. M. K. Geiling, R. Keith Cannan, and William Bloom, University of Chicago, April 28, 1944. Div. 9-523-M2
13. OSRD 3602. *Decontaminating Systems*, by J. E. Kirby, H. S. Rothrock, A. E. Barkdoll, C. T. Handy, and R. N. MacDonald, Chemical Department, E. I. du Pont de Nemours and Company, May 22, 1944. Div. 9-562-M4
14. OSRD 3782. *Improved Decontaminating Systems*, by J. E. Kirby, H. S. Rothrock, A. E. Barkdoll, C. T. Handy, and R. N. MacDonald, Chemical Department, E. I. du Pont de Nemours and Company, June 10, 1944. Div. 9-562-M5
15. OSRD 3927. *Improved Decontaminating Systems*, by J. E. Kirby, H. S. Rothrock, A. E. Barkdoll, C. T. Handy and R. N. MacDonald, Chemical Department, E. I. du Pont de Nemours and Company, August 1, 1944. Div. 9-562-M5
16. OSRD 4518. *Improved Decontaminating Systems. Chloramide Solvent Systems*, by J. E. Kirby, H. S. Rothrock, and A. E. Barkdoll, Chemical Department, E. I. du Pont de Nemours and Company, January 1, 1945. Div. 9-562-M6
17. OSRD 4523. *Improved Decontaminating Systems. Further Development of Oleate Paste Systems*, by J. E. Kirby, H. S. Rothrock, and R. N. MacDonald, Chemical Department, E. I. du Pont de Nemours and Company, January 1, 1945. Div. 9-562-M7
18. OSRD 4889. *A Study of the Decontamination of Surfaces Which Have Been Exposed to Chemical Warfare Agents — Special Study of the Decontamination and Regeneration of Carbon Fabrics*, by J. E. Kirby, H. S. Rothrock, C. T. Handy, and R. N. MacDonald, Chemical Department, E. I. du Pont de Nemours and Company, April 2, 1945. Div. 9-563-M1
19. OSRD 5025. *Thickening 30:60 Bleach/Water Slurries by Means of Asbestos*, by J. E. Kirby, H. S. Rothrock, and R. N. MacDonald, Chemical Department, E. I. du Pont de Nemours and Company, May 2, 1945. Div. 9-562-M8
20. OSRD 5389. *Decontamination Studies*, by J. E. Kirby, H. S. Rothrock, A. E. Barkdoll, C. T. Handy, R. N. MacDonald, F. C. McGrew, and J. C. Sauer, Chemical Department, E. I. du Pont de Nemours and Company, August 1, 1945. Div. 9-562-M9
21. OSRD 6111. *Preparation of the Chloramides, S-501, S-328, S-330, S-420, S-222, S-300, S-221, S-438 and Decontaminant 40*, by R. T. Major, W. H. Engels, J. R. Stevens, M. Tichler, W. Bartholomew, W. A. Bittenbender, S. W. Briggs, E. R. Braun, P. Chemicz, W. S. Clewell, P. C. Colin, and F. S. Wolf, Merck and Company, October 17, 1945. Div. 9-511.4-M3
22. OSRD 6300. *The Preparation of Isocyanates, Cyanuric Acid and Decontaminant 40*, by R. L. Jenkins and E. E. Hardy, Monsanto Chemical Company, December 31, 1945. Div. 9-223.3-M3

OSRD INFORMAL REPORT

23. Contract NDCrc-132, University of Chicago (University of Chicago Toxicity Laboratory). Inf. Month. Prog. Rept., NDRC 9:4:1-25, February 28, 1945. Div. 9-125-M2

MISCELLANEOUS

24. *Collection of Papers on Chemical Warfare*, edited by Roger Adams, Joseph Dee and W. C. Pierce, August 1, 1944. *III. Current Army and Navy Decontamination Practices*, by Jonathan W. Williams. Div. 9-10-M2

UNITED STATES ARMY REPORTS

War Department Manuals

25. FM 17-59. Armored Force Field Manual. *Decontamination of Armored Force Vehicles*, October 12, 1942.
26. FM 21-40. Basic Field Manual. *Defense against Chemical Attack*, September 7, 1942.

27. TM 3-220. War Department Technical Manual. *Decontamination*, November 15, 1943.
28. TM 3-221. War Department Technical Manual. *Decontaminating Apparatus M3A1*, April 15, 1943.
29. TM 3-222. War Department Technical Manual. *Decontaminating Apparatus M4*, February 5, 1944.

Chemical Warfare Service

30. Pamphlet No. 12. *Decontamination*, Chemical Warfare School, February 1942.
31. CMTR No. 20. *Examination of Captured German Weapon Decontaminating Set*, October 9, 1943.
32. CMTR No. 72. *German 3-Gal. Can of Decontaminating Bleach*, May 19, 1944.
33. CMTR No. 78. *Tin Box Containing Japanese Decontaminating Powder*, June 15, 1944.
34. TDMR 782. *Investigation of Methods for the Decontamination of Military Airplanes*, January 31, 1944.
35. TDMR 865. *A Visual Indicator Test Method for Evaluating Contact Hazard of Mustard Contaminated Surfaces*, September 26, 1944.
36. TDMR 871. *Surveillance of Bleaching Materials in Simulated Tropical Storage*, September 20, 1944.
37. TDMR 954. *Surveillance Tests of Apparatus, Decontaminating, 1½ Quart Capacity, M2*, January 18, 1945.
38. TDMR 1024. *Decontamination of Painted Metal Surfaces by Hot and Cold Water with or without Soap or Detergent*, April 7, 1945.

UNITED STATES NAVY REPORTS

Bureau of Naval Personnel

39. NAVPERS 15639. *Gas! Know Your Chemical Warfare*, January 1944.

Naval Research Laboratory

40. P-1944. *The Use of RH-195 for the Decontamination of HS and M-1*, October 8, 1942.
41. P-2125. *A Study of Perclene (Tetrachlorethylene) as a Solvent for Use in the Decontamination of Airplanes*, July 29, 1943.
42. P-2211. *Chloramide Paste Systems for Decontamination of Vesicants*, December 31, 1943.
43. P-2457. *Report on an Emulsion Paste System for Decontamination of Vesicants*, February 7, 1945.
44. P-2500. *Report on Correlation of Congo Red-S-328 and DB-3 Test Papers with Human Skin*, March 30, 1945.
45. C-877-2 (459-PCT). *The Reactions of Chloramides with Vesicants in Different Media, a Memorandum to the Director*, August 4, 1943.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

46. Porton Memorandum No. 11. *Decontamination of City Streets after a Mustard Gas Attack*, September 29, 1941.
47. Porton Memorandum No. 22. *Comprehensive Report on S*, March 5, 1943.
48. Porton Memorandum No. 28. *Methods of Decontamination*, April 15, 1944.
49. Porton Report No. 2231. *The Chemistry of Bromobenzyl Cyanide in Relation to the Development of Decontamination Methods*, July 2, 1941.
50. Porton Report No. 2404. *The Preparation and Examination of Methanesulfondichloramide*, August 11, 1942.
51. Porton Report No. 2331. *American and British Methods of Decontamination*, July 21, 1943.
52. Ptn. 800 (R.11120). *Decontamination Processes Applied to Vesicants Other Than Mustard*, September 10, 1941.
53. Ptn. 824 (R.12861). *Decontamination by the Steam Jenny*, November 11, 1941.
54. Ptn. 1400/1 (S.10270A). *Present Position of Impregnation, Decontamination, and Detection in North America*, July 28, 1942.
55. Ptn. 1416/1 (S.4665). *Captured German Equipment*, April 13, 1942.
56. Ptn. 2630 1 (C.6321) *Decontamination of A.F.V.'s Contaminated with CN*, May 23, 1944.
57. Ptn. 2644 (S.3380). *Decontamination of Roadways from Mustard Gas in the Presence of Rubble*, February 11, 1942.

Extramural Research

58. Oxford Biochemical Laboratory (R. A. Peters) Report No. 58 (W.5051). *Action of Chlorinating Agents on T.1023 ("S") in Chloroform*, by E. R. Holiday and A. G. Ogston, June 1942.

CANADIAN REPORT

Chemical Warfare Laboratories, Ottawa

59. Physiol. Sect. Rep. No. 23. *A Study of Vesicant Decontaminants*, August 25, 1943.

Chapter 34

OSRD FORMAL REPORTS

1. OSRD 124. *An Investigation of the Reactions between β,β'Dichlorethyl Sulfide, β'Chlorovinyl Dichloroarsine, Ethyl Dichloroarsine, Diphenylamine Chloroarsine and Certain Inorganic Ions*, by John H. Yoe, University of Virginia, August 23, 1941. Div. 9-422.8-M1
2. OSRD 125. *Studies on War Gas Detection and Analysis*, by John H. Yoe, University of Virginia, August 23, 1941.
3. OSRD 140. *I. Detection of Mustard Gas with 4-(p-nitrobenzyl) Pyridine. III. Catalytic Toxicity of Arsenical Gases*, by Weldon G. Brown, University of Chicago, September 22, 1941. Div. 9-115-M1
4. OSRD 165. *Paints, Powders and Papers for the Detection of Persistent Chemical Warfare Agents*, by W. C. Johnson, University of Chicago, November 4, 1941. Div. 9-411.1-M3
5. OSRD 177. *Development of Test Paper, Paint and Powder for the Persistent Agents*, by W. C. Fernelius and J. F. McReynolds, Ohio State University, November 14, 1941. Div. 9-411.1-M1

6. OSRD 493. *Detection of HS, M-1, ED or PD-1 with Trained Dogs and Rats*, by John H. Northrop, The Rockefeller Institute for Medical Research, April 10, 1942. Div. 9-422.8-M3
7. OSRD 503. *Methods for the Detection of Mustard Gas*, by Henry E. Bent, University of Missouri, April 15, 1942. Div. 9-422.113-M1
8. OSRD 505. *The Preparation of DB-3 Reagent*, by Weldon G. Brown, University of Chicago, April 15, 1942. Div. 9-411.2-M1
9. OSRD 506. *The Preparation of the DB-3 Reagent*, by Homer Adkins, University of Wisconsin, April 15, 1942. Div. 9-411.2-M2
10. OSRD 511. *Development of Test Paper, Paint and Powders for Persistent Agents and Test Papers for Their Oxidation Products*, by W. C. Fernelius and J. P. McReynolds, Ohio State University, April 17, 1942. Div. 9-411.1-M5
11. OSRD 681. *An Investigation of the Reaction of 1070 and 1130 with Certain Inorganic Ions and Detector Paints*, by John H. Yoe, University of Virginia, July 6, 1942. Div. 9-422.121-M2
12. OSRD 757. *An Investigation of Dyestuffs as Sensitive Agents for Detector Paint*, by John H. Yoe, University of Virginia, July 22, 1942. Div. 9-411.1-M6
13. OSRD 832. *Adaptation of the DB-3 Reagent for Field Detection*, by Weldon G. Brown, University of Chicago, August 21, 1942. Div. 9-422.13-M1
14. OSRD 879. *The Chemical Detection of 1130*, by D. S. Tarbell, University of Rochester, September 11, 1942. Div. 9-422.121-M3
15. OSRD 981. *Summary of Work on 1070, 1130 and Related Compounds in Section B-3, NDRC*, by C. S. Marvel, University of Illinois, October 22, 1942. Div. 9-221.2-M4
16. OSRD 1000. *Biological Methods for the Determination of M-1 and DH in Solutions and in Air*, by H. S. Gasser, The Rockefeller Institute for Medical Research, November 25, 1942. Div. 9-422.8-M8
17. OSRD 1116. *An Investigation of Organic Compounds as Indicators for the Vesicant Agents*, by John H. Yoe, University of Virginia, December 9, 1942. Div. 9-411.4-M1
18. OSRD 1401. *A Direct Specific Detector for Arsenical Vapors*, by R. S. Livingston, University of Chicago, May 11, 1943. Div. 9-422.23-M1
19. OSRD 1548. *Examination of the Thiocarbazones for Use in the Colorimetric Determination of Arsenicals*, by J. P. McReynolds, Ohio State University, June 29, 1943. Div. 9-422.21-M2
20. OSRD 1576. *Detection of Mustard by Hot-Wire or Furnace Oxidation and Rapid Analytical Determination of Arsenicals by Reaction with Thiocarbazones or by Oxidation with Dichromate*, by J. P. McReynolds, Ohio State University, July 8, 1943. Div. 9-422.8-M10
21. OSRD 1732. *Field Kit, Screening for the Detection of Chemical Warfare Agents in Water*, by A. M. Buswell, University of Illinois, August 30, 1943. Div. 9-412-M4
22. OSRD 1898. *The Identification of Samples of Agents Collected on Plain Silica Gel*, by R. S. Livingston, W. G. Brown, and W. C. Johnson, University of Chicago, October 11, 1943. Div. 9-421.2-M1
23. OSRD 3111. *Organic Reagents for L and ED*, by John H. Yoe and E. C. Coghill, University of Virginia, January 13, 1944. Div. 9-422.24-M2
24. OSRD 3670. *The Use of Thiocarbazones as Arsenical Detectors*, by D. S. Tarbell, C. W. Todd, M. C. Paulson, E. G. Lindstrom, and V. P. Wystrach, University of Rochester, May 24, 1944. Div. 9-422.21-M4
25. OSRD 4108. *Sensitivity of DB-3 Tube of M-9 Kit to Mustard at Various Concentrations in Air*, by F. H. MacDougall, D. J. Lehmicke, W. F. Johnson, Margaret Seiz, and T. C. Shields, University of Minnesota, September 7, 1944. Div. 9-422.114-M2
26. OSRD 4335. *Sensitivity of Arsenical Detector Tubes of M-9 Kits to L, PD and ED*, by F. H. MacDougall, D. J. Lehmicke, W. F. Johnson, Margaret Seiz, and T. C. Shields, University of Minnesota, November 9, 1944. Div. 9-422.23-M3
27. OSRD 4411. *Additional Observations on the Synthesis of Thiocarbazones, Especially DPT*, by D. S. Tarbell and E. G. Lindstrom, University of Rochester, November 30, 1944. Div. 9-411.4-M3
28. OSRD 4412. *Unsymmetrical Diarylethylenes as Detectors*, by D. S. Tarbell and E. G. Lindstrom, University of Rochester, November 30, 1944. Div. 9-411.4-M4
29. OSRD 4413. *Thioketones as Detectors for CW Agents*, by D. S. Tarbell and V. P. Wystrach, University of Rochester, November 30, 1944. Div. 9-411.4-M5
30. OSRD 4629. *A Systematic Scheme for the Detection of Toxics on Plain Silica Tubes*, by D. S. Tarbell, R. B. Carlin, V. P. Wystrach, E. Klingsberg, R. G. Bunnett, and E. G. Lindstrom, University of Rochester, January 24, 1945. Div. 9-421.2-M2
31. OSRD 4677. *The Reaction between DBT and Arsenicals*, by D. S. Tarbell and J. F. Bunnett, University of Rochester, January 31, 1945. Div. 9-422.21-M6
32. OSRD 4843. *The Detection of Organic Fluorine Toxics. The Use of Thiocarbazones as Arsenical Detectors*, by N. L. Drake, University of Maryland, April 19, 1945. Div. 9-422.8-M14
33. OSRD 5270. *A System for the Identification of Functional Groups Present in Chemical Warfare Agents*, by C. W. Gould, Jr., G. Holzman, J. W. Sease, E. H. Swift, and Carl Niemann, California Institute of Technology, June 26, 1945. Div. 9-420-M1

OSRD INFORMAL REPORTS

34. Contract OEMsr-79, University of Chicago, Weldon G. Brown.
    a. NDRC B-3-B Inf. Rept. No. 36. *The Detection of 1070 and 1130*, April 13, 1942. Div. 9-422.121-M1
    b. NDRC 9-3-1 Inf. Rept. No. 61. *Colorimetric Estimation of 1130 Vapor in Air Using DB-3 Silica Gel*, March 18, 1943. Div. 9-422.121-M5
    c. NDRC 9-3-1 Inf. Rept. No. 80. *Tetramethyldiaminodihydroanthracene Color Tests with CW Agents*, July 15, 1943. Div. 9-411.4-M2
    d. NDRC 9-3 Inf. Rept. No. 97. *Paper Tape Recording of CW Agents*, March 30, 1944. Div. 9-413.2-M2
    e. Inf. Month Prog. Rept. July 15, 1942. Div. 9-422.8-M5

f. Inf. Month. Prog. Rept. February 10, 1945. Div. 9-411.1-M8

g. Inf. Month. Prog. Rept. March 10, 1945. Div. 9-712.13-M3

h. Inf. Month. Prog. Rept. May 10, 1945. Div. 9-712.13-M3

35. Contract OEMsr-87, University of Chicago, Warren C. Johnson.

a. Tech. Rept. No. 2. *A Preliminary Study of Detector Paints and Powders*, March 14, 1941. Div. 9-411.1-M1

b. Tech. Rept. No. 5. *The Use of Dithizone as a Detector for M-1 and ED in the Vapor State*, March 28, 1941. Div. 9-422.21-M1

c. Tech. Rept. No. 20. *Detector Powder No. 1 (Brown)*, September 24, 1941. Div. 9-411.1-M2

d. NDRC B-3-B Inf. Rept. No. 50. *Note on the Detection of Dimethylfluophosphate*, November 13, 1942. Div. 9-422.31-M1

e. NDRC B-3-B Inf. Rept. No. 51. *Recommendations for the Detector Tubes to be Used in the Field Kit*, November 17, 1942. Div. 9-412.1-M1

f. NDRC B-3-B Inf. Rept. No. 51a. *Amendments and Additions to Recommendations for the Detector Tubes to be Used in the Field Kit*, November 30, 1942. Div. 9-412.1-M1

g. NDRC B-3-B Inf. Rept. No. 52. *Note on a Possible Indicator Paper for 1130*, November 17, 1942. Div. 9-422.121-M4

h. NDRC B-3-B Inf. Rept. No. 53. *A Catalyzed Low-Temperature Development of the DB-3 Test*, November 25, 1942. Div. 9-411.2-M3

i. NDRC 9-3-1 Inf. Rept. No. 57. *The Vapor Detector Kit*, January 26, 1943. Div. 9-412-M1

j. NDRC 9-3-1 Inf. Rept. No. 67. *The Effect of Temperature and Humidity on the Sensitivities of the Several Tubes of the Vapor Detector Kit, E4-R10*, April 1, 1943. Div. 9-412.1-M2

k. NDRC 9-3-1 Inf. Rept. No. 68. *The DB-3 Reagent in Tablet Form for Water Testing*, April 6, 1943. Div. 9-411.2-M4

l. NDRC 9-3-1 Inf. Rept. No. 71. *A Critical Comparison of Several Detectors for the Nitrogen Mustards*, April 27, 1943. Div. 9-422.12-M1

m. NDRC 9-3-1 Inf. Rept. No. 73. *Vapor Detection and Identification Equipment Designed for Use by the CWS*, May 7, 1943. Div. 9-412-M2

n. NDRC 9-3-1 Inf. Rept. No. 76. *The Sensitivities of the Tests of the Vapor Detector Kit, E5-R3, to Lethal and Casualty Producing Concentrations of Common Toxics*, May 27, 1943. Div. 9-412-M3

o. NDRC 9-3-1 Inf. Rept. No. 81. *Equipment for the Removal of Iron from Silica Gel*, July 26, 1943. Div. 9-411.3-M1

p. NDRC 9-3-1 Inf. Rept. No. 84. *Cuprous Iodide Impregnated Silica Gel as a Specific Detector for Lewisite*, September 4, 1943. Div. 9-422.23-M2

36. Contract OEMsr-139, University of Virginia, John H. Yoe.

a. NDRC B-3-B Inf. Rept. No. 38. *The Detection of Lewisite and Ethyldichlorarsine with Tetramethyldiaminodiphenylmethane*, April 17, 1942. Div. 9-422.24-M1

b. NDRC B-3-B Inf. Rept. No. 46. *Behavior of Thickened Vesicants with Detector Paints*, June 19, 1942. Div. 9-422.8-M6

37. Contract OEMsr-1092, University of Minnesota, F. H. MacDougall.

a. NDRC 9-3 Inf. Rept. No. 91. *Estimation and Control of the Acidity of Silica Gels*, January 11, 1944. Div. 9-411.3-M2

b. NDRC 9-3 Inf. Rept. No. 92. *Stability of CG Gels*, March 25, 1944. Div. 9-411.3-M3

c. NDRC 9-3 Inf. Rept. No. 96. *The Heating of Detector Tubes and the Temperatures Attained under Various Conditions*, May 12, 1944. Div. 9-412.1-M3

MISCELLANEOUS

38. NDRC Division 9 Report, *A Review of American, British, German, Japanese and Italian Field Detector Kits*, by Morris B. Jacobs, June 1944. Div. 9-412.2-M1

39. NDRC Division 9 Report, *Report of Conference Concerning the NRL Detector Kit*, by Morris B. Jacobs, July 7, 1944. Div. 9-412-M5

40. NDRC Division 9 Report, *Tabular Summary of British, Chinese, German, Japanese and Italian Field Detector Kits*, by Morris B. Jacobs, April 17, 1945. Div. 9-412.2-M2

UNITED STATES ARMY REPORTS

Chemical Warfare Service

41. CMTR 15. *Japanese Glass Ampoules of Detector Crystals*, August 1943.

42. CMTR 42. *German "Sniff Set." Riechprobenkasten*, December 1943.

43. CMTR-MIT 6. *Japanese Chemical Agent Detector Kit*, April 1, 1944.

44. CMTR-MIT 8. *German Chemical Agent Detector Kit*, April 19, 1944.

45. CMTR-MIT 9. *Japanese Naval Type Chemical Agent Detector Kit*, April 19, 1944.

46. Medical Division Rept. No. 1. *Miosis of the Pupil as a Test for Water Contamination by DF-3*, September 28, 1944.

47. Medical Division Rept. No. 2. *A Kit for the Detection of Blister Gases on Foods and Food Packaging Materials*, September 18, 1944.

48. Medical Division Rept. No. 7. *Field Testing of Spot Test Procedure for Detection of Fluoro-Organic Compounds in Water*, March 8, 1945.

49. Medical Division Rept. No. 31. *Sensitivity of Mustard and Arsenical Test Papers to Agents in Air and Water*, June 9, 1945.

50. MIT-MR 10. *Liquid Vesicant Detector Paper Containing R-1*, August 5, 1942.

51. MIT-MR 20. *Detector Crayons*, December 3, 1942.

52. MIT-MR 103. *Detector Papers for the Detection of Chemical Agent Vapors*, October 3, 1944.

53. MIT-MR 119. *DNB Test for Mustard Contaminated Impermeables*, December 15, 1944.
54. MIT-MR 131. *Improvement of Kit, Chemical Agent Detector, M-9 (July 1, 1943 July 1, 1944)*, May 5, 1945.
55. MIT-MR 145. *Detector Tubes for Kit, Chemical Agent Detector, M-9*, July 28, 1945.
56. MIT-MR 172. *Detector Crayons for Nitrogen Mustards*, September 8, 1945.
57. MRL(EA) Rept. No. 5. *The Use of Bismuth Iodide (Dragendorff) Papers for the Detection of Nitrogen Mustard*, October 28, 1943.
58. MRL(EA) Rept. No. 10. *The Microdetermination of HN-3 in Water*, January 21, 1944.
59. MRL(EA) Rept. No. 16. *Field Tests on Water Supplies Exposed to the Action of CG and AC*, January 17, 1944.
60. MRL(EA) Rept. No. 21. *Field Training of One Dog to Detect H*, May 2, 1944.
61. MRL(EA) Rept. No. 37. *A Test Paper for the Detection of Sulfur and Nitrogen Mustards on Foods and Food Packaging Materials*, September 18, 1944.
62. TDMR 314. *Chemical Agent Detector. Gas Detector Paint: Change in Formula to Meet Weathering Tests, and to Eliminate the Use of Cadmium Lithopone*, September 10, 1941.
63. TDMR 331. *Chemical Agent Detector. Gas Detector Crayon and Powder*, December 20, 1941.
64. TDMR 409. *Chemical Agent Detector. Detector Crayon for Nitrogen Mustards*, July 20, 1942.
65. TDMR 507. *Chemical Agent Detectors. Gas Absorption Type*, December 30, 1942.
66. TDMR 645. *Identification of the Nitrogen Mustards: An Improved Bismuth Potassium Iodide Reagent*, April 30, 1943.
67. TDMR 847. *Detection and Identification of Cyanides and Other Cyanogen Compounds: Pyrazalone-Pyridine Method*, June 1, 1944.
68. TDMR 882. *Kit, Chemical Agent Detector, M-9: An Investigation of the Tests Obtained with the Detector Tubes*, August 21, 1944.
69. TDMR 887. *Identification of Agents Containing Fluorine I. Use of Plain Silica Gel Tubes*, September 8, 1944.
70. TDMR 1010. *Phosgene Detector Paper*, March 19, 1945.
71. TDMR 1059. *Gamma Benzylpyridine-Barbituric Acid Reagent: A New Detector for CK*, May 14, 1945.
72. TDMR 1108. *Improvement of M-7 Vesicant Detector Crayon*, July 30, 1945.
73. Medical Research Laboratory (Edgewood Arsenal). Inf. Month. Prog. Repts.
    a. July 15, 1944.
    b. September 15, 1944.
    c. October 15, 1944.
    d. November 15, 1944.
    e. January 15, 1945.
    f. February 15, 1945.
    g. May 15, 1945.
    h. August 15, 1945.
74. CWS Report No. 125. *The Detection of Mustard Gas*, August 13, 1928.
75. CWS Technical Bulletin No. 3-7-1. *Methods and Equipment for the Detection of Vesicants*, June 30, 1942.
76. *Chemical Warfare Agents Detector Kit: For Use by Guard and Security Division*, March 13, 1944.

UNITED STATES NAVY REPORTS

Naval Research Laboratory

77. *A Laboratory Spot Test for the Nitrogen Mustards*, July 13, 1942.
78. *Protective Clothing*, August 31, 1942.
79. P-2223. *A Critical Evaluation of the Performance of the Army M-9 Chemical Warfare Agents Vapor Detection Kit*, January 28, 1944.
80. C-877-2(459-JEJ). *Tests of Liquid Vesicant Detectors*, February 12, 1944.
81. C-877-2(459-JAK). *An Improved Hydrocyanic Acid (AC) Detector Tube*, October 27, 1944.

MISCELLANEOUS

82. Navy Department, *Defensive Chemical Warfare Manual*, FTP 222, November 15, 1944.

BRITISH REPORTS

Chemical Defence Research Station, Porton

83. Porton Memorandum No. 22. *Comprehensive Report on S*, March 5, 1942.
84. Porton Memorandum No. 29. *Interim Memorandum on Gas Warfare in the Tropics*, November 21, 1944.
85. Porton Memorandum No. 30. *HN-3 as a CW Agent*, November 8, 1944.
86. Porton Report No. 2167. *A New Detector Paper Giving a Permanent Record of Exposure to Mustard Gas Vapor*, February 13, 1941.
87. Porton Report No. 2264. *Detector Papers for Vesicants*, September 10, 1941.
88. Porton Report No. 2371. *The Preparation of α-(β-Nitrobenzyl) Pyridine*, May 20, 1942.
89. Porton Report No. 2389. *Differential Detector Powders*, February 25, 1943.
90. Porton Report No. 2620. *Specific Test Papers for CW Agents*, May 9, 1944.
91. Porton Report No. 2629. *A Field Test for the Detection of Hydrogen Cyanide and Cyanogen Chloride in Post Mortem Material*, June 30, 1944.
92. Porton Report No. 2655. *The Reaction of Sodium Iodoplatinate with Mustard Gas and with the Nitrogen Vesicants*, February 1, 1945.
93. Ptn. 1205 (R.8016). *Estimation of H-Vapour Concentration by C.I.D.'s in the Field. Interim Report*, June 27, 1941.
94. Ptn. 1205/1 (P.9312). *A New Lewisite Detector Paper*, June 5, 1940.
95. Ptn. 1206 (P.9991). *A New Detector Paper for "H" and T-32 (Oxide-bis-β-chloroethyl Sulphide)*, June 14, 1940.
96. Ptn. 1208 (P.10058). *A Detector Paper for Trichlortriethylamine (T.777)*.
97. Ptn. 4024 (P.4059). *Detector Powder Trials*. April 1, 1944.
98. Ptn. 4034 (P.10923). *Detector, Vapour, Pocket, Mark I. Notes for Instructors*, August 22, 1942.

99. Ptn. 4036 (S.12386). *Detector Papers for S from Canada*, September 23, 1942.
100. Ptn. 4240 (V.3956) (A.3804 1 2 3 4). (1) *Substance T.2104, Interim Report.* (2) *Note on Some Experiments with the German War Gas T.2104*, May 30, 1945. (3) *Determination of the Vapour Pressure of T.2104*, April 23, 1945. (4) *New German Toxic Agent: Memorandum for The Chief, Chemical Warfare Service*, May 21, 1945. (V. 5600, V.5540) (A.3804, 5). (5) *Notes from Porton on the Identification and Detection of T.2104*, June 25, 1945.
101. Ptn. 4280 (T.14339). *Progress of Work on Fluoroacetates and Fluorophosphates, 1st Interim Report*, November 2, 1943.
102. Ptn. 4280 (T.16181). *The Detection of CW Agents Containing Fluorine, 2nd Interim Report*, December 4, 1943.
103. Ptn. 4280 (V.5007). *The Detection of CW Agents Containing Fluorine, 3rd Interim Report*, April 24, 1944.
104. Ptn. 4280 (V.9416). *The Detection of CW Agents Containing Fluorine, 4th Interim Report*, July 29, 1944.
105. Ptn. 4282 (T.4396A). *A Method for the Detection of Methyl Fluoroacetate in Dilute Aqueous Solution*, forwarded by Chemical Board, April 5, 1943.

Extramural Research

106. Imperial College of Science and Technology (H. V. A. Briscoe).
   a. (V.3440). *The Analysis of Organic Fluoro Compounds, Modifications of the De Boer Zirconium-Alizarin Reagent*, by V. A. Briscoe and H. J. Emeleus, April 15, 1942
   b. (V.16841). *The Detection of Volatile Fluorine Containing Compounds*, forwarded by the Chemical Board, November 29, 1943.

MISCELLANEOUS

107. (V.19840). *Use of No. 2 Detector Paper (SD) in H - Determination of Long Period Contact Persistence of H*, January 28, 1942.
108. (V.19955). *Monthly Liaison Letter*, January 1941.
109. (Z.6459). *A Specific Test for H*, June 19, 1944
110. Ministry of Home Security. *SD Method for the Detection of Mustard Gas Vapour*, 1942.
111. *Further Notes on S.* Abstract from Notes of Meeting of Chemical Factories Medical Subcommittee, held at Ministry of Supply, Adelphi, April 15, 1942.
112. Report No. V.2000. (III-1-790). *A Summary and Review of the Potentialities of the Various Test Papers Proposed for S*, Canadian Military Headquarters, London, April 8, 1943.
113. Report No. V.23783. *Notes on Work Carried Out under the Direction of the Chemical Defence Board in Australia*, October 25, 1943 January 25, 1944.

CANADIAN REPORTS

Extramural Research

114. C.E. 116 No. (III-1-823), May 10, 1943. *The Detection of S and T.???*, by M. M. Marshall, L. A. Cox and C. Moran, University of British Columbia, Vancouver, B. C.
115. C.E. 118 No. (III-1-289), July 9, 1942. *Detection of S*, by F. E. Beamish, H. A. Bewick, J. E. Currah, A. J. Cruikshank and G. M. Allison, University of Toronto.
116. C.E. 118 No. (III-1-316), August 3, 1942. *Detection of S*, Progress Report on C.E. 118, by F. E. Beamish, H. A. Bewick, J. E. Currah, A. J. Cruikshank, University of Toronto.
117. C.E. 118 No. (III-1-330), August 15, 1942. *The Detection of S*, by F. E. Beamish, H. A. Bewick, J. E. Currah, A. J. Cruikshank, University of Toronto.
118. C.E. 118 No. (III-1-341), September 3, 1942. *The Detection of S*, by F. E. Beamish, H. A. Bewick, J. E. Currah, A. J. Cruikshank, University of Toronto.
119. C.E. 134 No. (III-1-476), November 30, 1942. *The Detection of Z*, by F. E. Beamish, J. E. Currah, A. J. Cruikshank and A. A. Sheppard, University of Toronto.
120. C.E. 134 No. (III-1-509), December 15, 1942. *The Detection of Z*, by F. E. Beamish, J. E. Currah, R. W. Jackson and A. A. Sheppard, University of Toronto.
121. C.E. 152 No. (III-1-792), April 7, 1943. *Detection of S, M, and HS*, by F. E. Beamish, J. E. Currah, A. A. Sheppard and J. R. Mills, University of Toronto.
122. C.E. 152 No. (III-1-1044), August 26, 1943. *The Detection of L*, by F. E. Beamish, J. E. Currah and M. K. Phibbs, University of Toronto.
123. C.E. 152 No. (III-1-1295), November 10, 1943. *The Detection of L*, by F. E. Beamish, A. C. Sibbald, R. E. Thiers and J. E. Currah, University of Toronto.
124. C.E. 152 No. (III-1-1402), December 8, 1943. *The Stabilization of Impregnite Papers for the Determination of H*, by F. E. Beamish, J. E. Currah, R. E. Thiers, E. M. Arthur and A. C. Sibbald, University of Toronto.
125. C.E. 152 No. (III-1-1511), January 31, 1944. *The Detection of L*, by F. E. Beamish, J. E. Currah and A. C. Sibbald, University of Toronto.

Chemical Warfare Laboratories, Ottawa

126. Appendix to Res. Rept. No. 10 (III-1-329). *Notes Regarding the Field Use of the Dragendorff Type Detector for S*, forwarded by National Research Council, Ottawa, Canada.
127. Res. Sect. Rept. No. 35 (III-1-1567). *Canadian Modification of Case, Water Testing, Poisons*, November 25, 1943.
128. Rept. No. III-1-301. *Series of Reports (7) on S Issued by Experimental Station, Suffield, University of Alberta, and Chemical Warfare Laboratories, Ottawa*, July 1942.

AUSTRALIAN REPORT

129. CD (Australia) Note No. 44. *The Deterioration of Spotted SD Papers under Simulated Tropical Conditions*, May 11, 1945.

INDIAN REPORTS

130. CDRE (India) Rept. No. 251. *The Correlation of the SD Test with the Vesicant Activity of Contaminated Soil and the Persistence of H Mixtures in Soil under Indian Hot Weather Conditions*, February 20, 1943.
131. CDRE (India) Note No. 29/43. *A Field Detector for Mustard Gas*, January 6, 1943.

132. Circular No. Tech. 1 1943 (M O India No. 1148). *Stability of Reagents for SD Test for Mustard Gas*, January 20, 1943.

OPEN LITERATURE

133. Schroeter, Angew. Chem., **46**, 164, 1936.
134. Grignard, Rivat and Scratelard. Ann. chim., **15**, 5, 1921.
135. Cox. Analyst, **64**, 807, 1939.
136. Yaldick, Perrott and Furman. J. Am. Chem. Soc., **42**, 266, 1920.
137. Sartori. *The War Gases*, D. van Nostrand, New York, 1940.
138. Jacobs. *War Gases*, Interscience, New York, 1942.

Chapter 35

OSRD FORMAL REPORTS

1. OSRD 1806. *The Identification of Samples of Agents Collected on Plain Silica Gel*, by R. S. Livingston, University of Chicago, October 11, 1943. Div. 9-421.2-M1
2. OSRD 3459. *Microscopical Identification of Solid Chemical Warfare Agents*, by C. W. Mason, F. A. Hamm, G. B. DeLaMater, Cornell University, April 12, 1944. Div. 9-421.1-M1
3. OSRD 3658. *Microscopical Identification of Explosives*, by C. W. Mason, Cornell University, May 22, 1944. Div. 9-420-M1
4. OSRD 3663. *A System for the Ultimate Analysis of Chemical Warfare Agents Part I, Fusion of the Sample and Part II, The System of Analysis for the Acidic Elements*, by E. H. Swift and Carl Niemann, California Institute of Technology, May 29, 1944. Div. 9-421.3-M1
5. OSRD 3804. *Drop Reactions for the Microscopical Identification of Arsenical Chemical Warfare Agents*, by C. W. Mason, Cornell University, May 22, 1944. Div. 9-422.2-M1
6. OSRD 3820. *The Analysis of Smokes*, by Henry E. Bent and Anna Jane Harrison, University of Missouri, June 3, 1944. Div. 9-422.6-M1
7. OSRD 3993. *Microscopical Properties of Oxidation Derivatives of Arsenicals*, by C. W. Mason, G. B. DeLaMater, and F. A. Hamm, Cornell University, August 9, 1944. Div. 9-213-M8
8. OSRD 3994. *Drop Reactions for the Microscopical Identification of Nitrogen Mustards*, by C. W. Mason and G. B. DeLaMater, Cornell University, August 9, 1944. Div. 9-422.12-M2
9. OSRD 3995. *Microscopical Properties of Derivatives of Nitrogen Mustards with Picric Acid*, by C. W. Mason, G. B. DeLaMater, and F. A. Hamm, Cornell University, August 9, 1944. Div. 9-221.1-M14
10. OSRD 3998. *Microscopical Properties of Derivatives of Arsenicals with N-Pentamethylenedithiocarbamate*, by C. W. Mason and G. B. DeLaMater, Cornell University, August 9, 1944. Div. 9-213-M9
11. OSRD 4107. *Microscopical Properties of Derivatives of H, Q and Related Compounds with Palladous Chloride*, by C. W. Mason and G. B. DeLaMater, Cornell University, September 7, 1944. Div. 9-421.1-M2
12. OSRD 4300. *The Microscopical Identification of Chloropicrin*, by C. W. Mason, Cornell University, November 3, 1944. Div. 9-422.3-M1
13. OSRD 4470. *Microscopical Properties of 2,4-Dinitrophenylhydrazine Derivatives of Certain Chemical Warfare Agents*, by C. W. Mason and G. B. DeLaMater, Cornell University, December 15, 1944. Div. 9-226-M1
14. OSRD 4620. *A Systematic Scheme for the Detection of Toxics on Plain Silica Tubes*, by L. S. Tarbell, R. B. Carlin, V. P. Wystrach, E. Klingsberg, R. F. Bunnett, and E. G. Lindstrom, University of Rochester, January 24, 1945. Div. 9-421.2-M2
15. OSRD 4678. *The Microscopical Identification of Derivatives of Certain Chemical Warfare Agents*, by C. W. Mason and G. B. DeLaMater, Cornell University, February 8, 1945. Div. 9-421.1-M3
16. OSRD 4716. *Microscopical Properties of Derivatives of Fluorine Agents*, by C. W. Mason, Cornell University, February 15, 1945. Div. 9-252-M5
17. OSRD 4727. *Microscopical Identification of Derivatives of Chemical Warfare Agents*, by C. W. Mason, Cornell University, February 22, 1945. Div. 9-421.1-M4
18. OSRD 4837. *Micro Reactions for the Identification of Fluorophosphates*, by C. W. Mason, Cornell University, March 21, 1945. Div. 9-422.31-M2
19. OSRD 4838. *Microscopical Identification of Chemical Warfare Agents and Their Derivatives*, by C. W. Mason, Cornell University, March 21, 1945. Div. 9-421.1-M5
20. OSRD 4987. *The Analysis of Smokes*, by Henry E. Bent and Anna Jane Harrison, University of Missouri, April 25, 1945. Div. 9-422.6-M2
21. OSRD 5075. *Appendices to a System for the Ultimate Analysis of Chemical Warfare Agents*, by E. H. Swift and Carl Niemann, California Institute of Technology, May 17, 1945. Div. 9-400-M1
22. OSRD 5076. *Qualitative Tests for Certain Acidic Elements in Organic Compounds*, by E. H. Swift, Carl Niemann, Edward Bennett, Clark Gould, Jr., California Institute of Technology, May 17, 1945. Div. 9-421.3-M2
23. OSRD 5077. *A System for the Separation and Purification of Decigram Quantities of Chemical Warfare Agents*, by C. W. Gould, Jr., G. Holzman, E. H. Swift, and Carl Niemann, California Institute of Technology, May 17, 1945. Div. 9-414-M2
24. OSRD 5270. *A System for the Identification of Functional Groups Present in Chemical Warfare Agents*, by Clark W. Gould, Jr., George Holzman, John W. Sease, and Carl Niemann, California Institute of Technology, June 26, 1945. Div. 9-415-M1
25. OSRD 5430. *A System for the Ultimate Analysis of Chemical Warfare Agents, Part III*, by E. H. Swift and Carl Niemann, California Institute of Technology, August 10, 1945. Div. 9-421.2-M3
26. OSRD 5434. *A Course of Instruction for the Personnel of the Ultimate Analysis Section of the M-2 Chemical Laboratory Company*, by E. H. Swift and Carl Niemann, California Institute of Technology, August 10, 1945. Div. 9-414-M3
27. OSRD 6046. *A Syringe Microburet*, by P. S. Farrington, P. A. Shaffer, Jr., E. H. Swift, and Carl Niemann,

4. OSRD 4627. *The Recovery of H Vapor from Air by Bubblers Containing 50% Acetic Acid, Diethyl Phthalate, 0.5 N Sulfuric Acid, Ethanol or Pyridine B*, by Clark Gould, Carl Reckemann, Phillip Shaffer, Jr., John Brockman, George Holzman, Thomas Lee, E. H. Swift, and Carl Niemann, California Institute of Technology, January 25, 1945. Div. 9-422.117-M1
5. OSRD 5470. *Field Sampling of H Vapor with Tape Recorders*, by D. E. Pearson, R. J. Stell, K. E. Wilzbach, H. E. Heller, E. G. Ballweber, R. F. Nystrom, and W. G. Brown, University of Chicago, August 17, 1945. Div. 9-422.111-M2
6. OSRD 6042. *The Stainless-Steel Propane Injector*, by Arnold O. Beckman, James D. McCullough, and Robert Cruse, National Technical Laboratories, September 13, 1945. Div. 9-414.1-M2
7. OSRD 6045. *A Recording Field Sight*, by A. Briglio, J. Brockman, Jr., W. Schlinger, P. A. Shaffer, Jr., E. H. Swift, and Carl Niemann, California Institute of Technology, September 5, 1945. Div. 9-413.3-M3
8. OSRD 6047. *A Semivariable Air Pump*, by A. Briglio, J. Brockman, Jr., W. Schlinger, P. A. Shaffer, Jr., E. H. Swift, and Carl Niemann, California Institute of Technology, September 5, 1945. Div. 9-413.11-M2
9. OSRD 6119. *The Collection and Separation of Samples of Persistent Agents from Contaminated Materials Other Than Air*, by David Brown, Edward L. Bennett, E. H. Swift, and Carl Niemann, California Institute of Technology, October 16, 1945. Div. 9-400-M2
10. OSRD 6185. *A Study of Turbulent Diffusion of Gas Clouds Over Several Terrains*, by Harold Johnston, Robert Merrill, Robert Mills, and Carl Niemann, California Institute of Technology, January 28, 1946. Div. 9-413.3-M4

OSRD INFORMAL REPORT

11. Contract NDCrc-132, University of Chicago Toxicity Laboratory, E. M. K. Geiling, Inf. Month Prog. Repts. on *Toxicity of Chemical Warfare Agents*, NDRC 9:41. Div. 9-125-M2
    a. No. 20, September 10, 1944.
    b. No. 21, October 10, 1944.

UNITED STATES ARMY REPORTS

Chemical Warfare Service

12. DPGSR 20. *Field Thickening of Levinstein Mustards*, April 3, 1944.
13. DPGSR 45. *The Sampling of Mustard Vapor*, March 1, 1945.
14. DPGFPR 2. *Sampling of Mustard Vapor by Means of Bubblers at Flow Rates of Ten Liters per Minute*, May 3, 1944.
15. EACD 123. *Gas Sampling Machine*, March 27, 1922.
16. EACD 167. *Sampling and Analysis of Mustard Gas in Field Tests*, May 15, 1922.
17. EACD 233. *Sampling and Analysis of Mustard Gas in Field Tests, Charcoal Method*, November 1922.
18. MRIAEA) Rept. No. 23. *Correlation of Eye Changes in Rabbits with CT Exposure to H*, June 12, 1944.
19. SIPR 5. *The Sampling of Mustard Vapor in Tropical Jungle*, July 15, 1944.
20. TDMR 525. *Methods of Analysis and Detection of Chemical Agents, Methods for Field Sampling and Analysis of MS Vapors in Air*, January 14, 1943.
21. TDMR 1038. *A Field Method for Removing Chlorine and Chlorinating Agents That Interfere with the Estimation of Total Dosages of H*, April 11, 1945.

BRITISH REPORTS

Chemical Defence Research Station, Porton

22. Porton Memorandum No. 19. *Chemical Sampling of Chemical Warfare Agents in Field Experiments*, October 17, 1942.
23. Porton Memorandum No. 25. *The Sampling and Analysis of Initial Clouds*, October 7, 1943.
24. Porton Report No. 2280. *The Effects of Mustard on Cities*, October 2, 1941.
25. Porton Report No. 2304. *The Effects of Mustard Gas on Cities*, November 24, 1941.
26. Porton Report No. 2479. *The Estimation of Dyed Charges Part I. Unthickened Charges on Turf*, February 17, 1943.
27. Porton Report No. 2507. *Drop Trap Methods for the Chemical Sampling of Initial Clouds*, August 20, 1943.
28. Porton Report No. 2515. *Memorandum of the Persistence of, and Vapour Concentrations from, C. W. Agents When Dispersed on the Ground*, June 23, 1943, and *Addenda*, July 3, 1944.
29. Porton Report No. 2517. *The Estimation of Dyed Charges Part II. Unthickened Production HS. Part III. Thickened Charges*, July 29, 1943.
30. Porton Report No. 2521. *The Fibre-Glass Micro Filter, an Improved Device for Sampling Certain Types of Particulate Clouds*, July 21, 1943.
31. Porton Report No. 2578. *Assessment of the U.S.A. 155 mm Howitzer HS Shell*, December 8, 1943.
32. Porton Report No. 2585. *The Estimation of Dyed Charges Part IV. Use of Oil Yellow (C.I. No. 19) as Characterizer*, March 14, 1944.
33. Porton Report No. 2613. *The Application of Characterizers to the Estimation of Cloud Samples on Cascade Impactor Plates*, April 20, 1944.
34. Porton Report No. 2619. *The Detection and Estimation of Minute Concentrations of H in Factory Air*, June 1, 1944.
35. Porton Report No. 2664. *The Sampling of H Vapour on Solid Absorbents*, February 1, 1945.
36. Ptn. 1600 (T.3807). *A Modified Bubbler for Field Sampling*, July 31, 1944.
37. Ptn. 1601 2 (T.3816). *Penetration of Droplets through Bubblers*, November 10, 1942.
38. Ptn. 1708 (T.12258). *Sampling of Particulate Clouds with Impingers*, October 25, 1943.

CANADIAN REPORTS

Experimental Station, Suffield, Alberta

39. Suffield Report No. 48. *Heavy Mustard Contamination of a Small Area*, December 30, 1942.

40. Suffield Report No. 49. *The Assessment of the U.S. 105 mm and 155 mm Shell*, February 3, 1943.
41. Suffield Report No. 92. *Vapour Danger from Gross Mustard Contamination*, October 8, 1943.
42. Suffield Report No. 98. *The Physiological Activity of the Cloud Produced by the Coming's H Thermal Generator*, November 25, 1943.
43. Suffield Report No. 123. *Determination of the Minimum Number of Sampling Points Required to Give a True Picture of the Vapor Hazard in a Large Area Contaminated with Mustard Gas*, December 18, 1944.
44. Suffield Technical Minute No. 3. *Filter Paper Assemblies for Estimating Ground Contamination from Bursting Chemical Weapons*, September 23, 1942.
45. Suffield Technical Minute No. 42. *Field Assessment of Mustard Thickened with Polymethyl Methacrylate*, December 14, 1943.
46. Suffield Technical Minute No. 63. *The Use of Impingers for Sampling Particulate Clouds*, July 1, 1944.
47. Suffield Technical Minute No. [illegible]. *The Determination of H in Drops of Dyed Charging*, July 15, 1944.
48. Suffield Technical Minute No. 67. *The Estimation of Ground Contamination, Earth Sampling Method*, July 20, 1944.
49. Suffield Technical Minute No. 77. *Summary and Review of Present Methods of Field Sampling and Analysis for CW Agents*, October 23, 1944.
50. Suffield Technical Minute No. 91. *A New Design of Bead Bubbler*, April 17, 1945.
51. Suffield Technical Minute No. 101. *Test of the Stainless Steel Propane Injector*, June 22, 1945.

AUSTRALIAN REPORTS

52. CD (Australia) Rept. No. 26. *The Sampling and Analysis of Mustard Gas Vapor under Tropical Conditions*, April 1, 1944.
53. CD (Australia) Rept. No. 51. *The Performance of the M47A2 Mustard Bomb in Tropical Jungle. Assessment of Vapor Effects of Individual Bombs*, July 27, 1944.
54. CD (Australia) Note No. 31. *A Note on the Effects of Acetone, Methanol and Diethyl Ether on the Determination of Mustard by the Iodoplatinate, and Bromine Titration Methods*, October 9, 1944.
55. CD (Australia) Note No. 46. *A Modified Bubbler for Field Sampling*, May 14, 1945.
56. CD (Australia) Note No. 54. *Estimation of Mustard Gas in the Presence of Bleach*, June 16, 1945.

Chapter 37

OSRD FORMAL REPORTS

1. OSRD 516. *Volumetric Methods for the Determination of Small Quantities of HS, Q, T, M-1, ED, DM and PDA*, by J. H. Northrop, The Rockefeller Institute for Medical Research, April 20, 1942.
2. OSRD 723. *The Hydrolysis of β,β' Dichlorodiethyl Sulfide in the Vapor Phase. The Quantitative Estimation of β,β' Dichlorodiethyl Sulfide in Solution*, by C. C. Price, University of Illinois, June 15, 1942. Div. 9-212.112-M2
3. OSRD 864. *Titration of HS, Q, T, M-1, ED and PDA with Hypochlorite and Methyl Red*, by J. H. Northrop, The Rockefeller Institute for Medical Research, September 7, 1942.
4. OSRD 870. *The Chemical Detection of 1120*, by D. S. Tarbell, University of Rochester, September 11, 1942.
5. OSRD 1547. *Determination of Arsenicals by a Dichromate Volumetric Method*, by J. P. McReynolds, Ohio State University, June 20, 1943. Div. 9-422.22-M1
6. OSRD 3480. *Colorimetric Determination of Fluorine in Fluoro-Organic Compounds*, by J. H. Yoe and L. G. Overholser, University of Virginia, April 14, 1944. Div. 9-422.3-M1
7. OSRD 3481. *Determination of Fluorine in Fluoro-Organic Compounds*, by J. H. Yoe, J. M. Salsbury and J. W. Cole, University of Virginia, April 14, 1944. Div. 9-422.3-M2
8. OSRD 3693. *A System for the Ultimate Analysis of Chemical Warfare Agents, Parts I and II*, by E. H. Swift and Carl Niemann, California Institute of Technology, May 29, 1944.
9. OSRD 3914. *Studies on the Determination of the Acidity of CC*, by J. H. Yoe and L. G. Overholser, University of Virginia, July 18, 1944. Div. 9-223.1-M2
10. OSRD 4153. *The Determination of HN-3 (and of H) by a Mercurimetric Titration of Hydrolyzed Chloride*, by T. Lee, E. H. Swift, and Carl Niemann, California Institute of Technology, September 21, 1944. Div. 9-422.13-M3
11. OSRD 4154. *The Behavior of Compounds Related to H in the Bromine, Chloramine-T, Iodoplatinate, Mercurimetric and DB-3 Methods for the Determination of H*, by G. Holzman, T. Lee, J. W. Sease, E. H. Swift, and Carl Niemann, California Institute of Technology, September 20, 1944. Div. 9-422.118-M2
12. OSRD 4158. *Gravimetric Determination of Water, Trimer and Residue in Cyanogen Chloride*, by J. H. Yoe and C. H. Lindsley, University of Virginia, September 21, 1944. Div. 9-223.1-M4
13. OSRD 4288. *The Colorimetric Estimation of H and HN-3 with DB-3*, by G. Holzman, E. H. Swift, and Carl Niemann, California Institute of Technology, October 27, 1944. Div. 9-422.13-M5
14. OSRD 4410. *Determination of Water in Hydrocyanic Acid*, by J. H. Yoe and C. H. Lindsley, University of Virginia, November 30, 1944. Div. 9-223.2-M1
15. OSRD 4414. *Determination of Fluorine in Certain Fluoro-Organic Compounds in Water*, by J. H. Yoe, J. M. Salsbury, and J. W. Cole, University of Virginia, November 30, 1944. Div. 9-422.3-M4
16. OSRD 4494. *Determination of Iron in CK, Cyanuric Chloride and CK Polymer*, by J. H. Yoe, L. G. Overholser, and A. R. Armstrong, University of Virginia, December 22, 1944. Div. 9-223.1-M6
17. OSRD 4600. *A Study of the Iodoplatinate Method for the Determination of H in 50% Acetic Acid*, by J. W. Sease, E. H. Swift, and Carl Niemann, California Institute of Technology, January 18, 1945. Div. 9-422.116-M1
18. OSRD 4679. *The Volumetric Determination of H by Means of Chloramine-T or Other Oxidizing Agents*, by

T. Lee, E. H. Swift, and C. Niemann, California Institute of Technology, February 6, 1945.
Div. 9-422.115-M4

19. OSRD 4000. *A Study of the Chloramine-T-o-Tolidine Method for the Determination of H in 50% Acetic Acid*, by J. W. Sease, E. H. Swift, and Carl Niemann, California Institute of Technology, February 1, 1945.
Div. 9-422.115-M3

20. OSRD 4843. *The Detection of Organic Fluorine Vapors — The Use of Thiocarbamates as Arsenical Detectors*, by N. L. Drake, University of Maryland, March 8, 1945.
Div. 9-422.8-M14

21. OSRD 4990. *Fractionation of Residues from Degradation of Cyanogen Chloride*, by J. H. Yoe, C. H. Lindsley and A. R. Armstrong, University of Virginia, April 26, 1945.
Div. 9-223.1-M7

22. OSRD 5151. *The Sampling and Estimation of AC in the Presence of Titanium Tetrachloride, Chlorsulfonic Acid and Sulfur Trioxide Smokes*, by George Holzman, E. H. Swift, and Carl Niemann, California Institute of Technology, August 17, 1945. Div. 9-422.42-M1

OSRD INFORMAL REPORTS

23. Contract NDCrc-132, University of Chicago Toxicity Laboratory, E. M. K. Geiling. Inf. Month. Prog. Repts. on *Toxicity of Chemical Warfare Agents*, NDRC 9:1:1.
Div. 9-125-M2
   a. No. 1, February 10, 1943.
   b. No. 4, May 10, 1943.
   c. No. 12, January 10, 1944.
   d. No. 22, November 10, 1944.
   e. No. 23, December 10, 1944.
   f. No. 25, February 28, 1945.

24. Contract OEMsr-70, University of Chicago, W. G. Brown. NDRC Section 9:3. Inf. Rept. No. 61, *Colorimetric Estimation of 1149 Vapor in Air Using DB-3 Silica Gel*, by R. G. Denkewalter and W. R. Remington, March 18, 1943. Div. 9-422.121-M5

25. Contract OEMsr-325, California Institute of Technology, E. H. Swift and Carl Niemann. Inf. Month. Prog. Repts.
Div. 9-121-M1
   a. August 10, 1945.
   b. September 10, 1945.

26. Contract OEMsr-363, University of Illinois, C. C. Price. Inf. Month. Prog. Repts. Div. 9-422.8-M11
   a. June 10, 1944.
   b. July 10, 1944.
   c. August 10, 1944.

27. Contract OEMcmr-24, The Johns Hopkins University, A. C. Woods and J. S. Friedenwald. *Estimation of HS and of Activated HS with the Aid of DB-3*, November 23, 1942.
Div. 9-422.114-M1

28. Contract OEMcmr-108, University of Pennsylvania, D. Wright Wilson and Harry M. Vars.
   a. *The Quantitative Colorimetric (Photometric) Determination of HS, 1130 and 1070 with the DB-3 Reagent*, by D. W. Wilson, S. Gurin, and D. I. Crandall, October 19, 1942. Div. 9-422.13-M2
   b. *The Quantitative Determination of N-Mustards and H in Foods by Means of the DB-3 Method*, by D. W. Wilson, H. M. Vars, E. D. Gjessing, D. I. Crandall, and S. Gurin, October 25, 1944.
Div. 9-422.13-M4

29. Contract OEMcmr-141, Harvard University, D. G. Cogan.
   a. *Methods for the Distinction and Determination of H and Semi-H*, by D. G. Cogan, V. E. Kinsey, and W. M. Grant, January 20, 1943.
Div. 9-422.118-M1
   b. *A Simple Quantitative Micro Test for HS*, by D. G. Cogan, V. E. Kinsey, and W. M. Grant, July 17, 1942. Div. 9-422.115-M1
   c. *A Method for Increasing the Sensitivity of Micro-Determination of HS*, by D. G. Cogan, V. E. Kinsey, and W. M. Grant, August 4, 1942.
Div. 9-422.115-M2

UNITED STATES ARMY REPORTS

Chemical Warfare Service

30. DPGSR 42. *The Behavior of CNS Dispersed from M47A2 Bombs in Wooded Terrain under Semi-Tropical Conditions*, December 5, 1944.

31. DPGSR 45. *The Sampling of Mustard Vapor*, March 1, 1944.

32. EACD 167. *Sampling and Analysis of Mustard Gas in Field Tests*, May 15, 1922.

33. EACD 233. *Sampling and Analysis of Mustard Gas in Field Test, Charcoal Method*, November 1922.

34. Med. Div. Rept. No. 6. *The Detection of Organic Fluorine Compounds in Water*, October 31, 1944.

35. MRL(EA) Rept. No. 37. *A Test Paper for the Detection of Sulfur and Nitrogen Mustards on Foods and Food Packaging Materials*, September 18, 1944.

36. TDMR 525. *Methods of Analysis and Detection of Chemical Agents, Method for Field Sampling and Analysis of MS Vapors in Air*, January 14, 1943.

37. TDMR 613. *Quantitative Determination of Fluorophosphates*, April 7, 1943.

38. TDMR 734. *Methods of Analysis of Nitrogen Mustards and Glycol Amines*, September 17, 1943.

39. TDMR 735. *New Methods of Analysis for Chemical Warfare Agents: The DB-3 Silica Gel Method for the Estimation of HN1, HN2 and HN3 in Vapour Samples*, October 16, 1943.

40. TDMR 761. *Methods of Analysis of L Prepared by the Cuprous Chloride and Mercuric Chloride Processes*, November 1, 1943.

41. TDMR 1123. *Compound MCE Estimation of Concentrations in Air and Sorption by Charcoal* August 21, 1945.

42. Dugway Proving Ground Medical Research Laboratory Weekly Reports.
   a. No. 21, August 23, 1944.
   b. No. 27, October 4, 1944.

43. Toxicological Research Laboratory, Edgewood Arsenal. Inf. Month. Prog. Rept. No. 1, July 1944.

44. ETF 107.432-1. *Tentative Method for Analysis of Total Dosage MCE Field Samples*, June 9, 1945.

UNITED STATES NAVY REPORT

Naval Research Laboratory

45. P-2510. *Methods for the Determination of the Vesicant Content of Contaminated Carbon Clothing*, June 20, 1945.

BRITISH REPORTS

Chemical Defence Experimental Station, Porton

46. Porton Memorandum No. 17. *Standard Methods of Test (Chemical and Physical) Employed in Chemical Warfare Investigations*, March 7, 1942.
47. Porton Memorandum No. 19. *Chemical Sampling of Chemical Warfare Agents in Field Experiments*, October 17, 1942.
48. Porton Memorandum No. 25. *The Sampling and Analysis of Initial Clouds*, October 7, 1943.
49. Porton Memorandum No. 30. *HN-3 as a Chemical Warfare Agent*, November 8, 1944.
50. Porton Report No. 2372. *Estimation of T.773 in Field and Chamber Samples*, September 21, 1942.
51. Porton Report No. 2405. *A Routine Method of Analysis for S*, August 24, 1942.
52. Porton Report No. 2412. *Investigation of the Estimation of S by the γ-(p-Nitrobenzyl) Pyridine Method, with Particular Reference to Its Stability in Acid Solution*, September 1, 1942.
53. Porton Report No. 2423. *Estimation of Chlorine by Titration with Mercuric Nitrate with Particular Reference to the Estimation of Phosgene*, September 7, 1942.
54. Porton Report No. 2477. *Colorimetric Method for the Estimation of H Using Chloramine T*, February 17, 1943.
55. Porton Report No. 2492. *An Accurate Method for the Determination of Mustard Vapor Concentrations*, March 10, 1943.
56. Porton Report No. 2549. *New Titrimetric Method for the Estimation of Fluorine*, October 8, 1943.
57. Porton Report No. 2556 *Estimation of Organic-Fluorine Compounds. Part I. Methyl Fluoroacetate (T.1302)*, October 27, 1943.
58. Porton Report No. 2557 *Estimation of Organic Fluorine Compounds. Part II. Dialkyl Fluorophosphates*, February 4, 1944.
59. Porton Report No. 2619. *The Detection and Estimation of Minute Concentrations of H in Factory Air*, June 1, 1944.
60. Porton Report No. 2656. *The Reaction of Sodium Iodoplatinate with Mustard Gas and with the Nitrogen Vesicants*, February 1, 1945.
61. Ptn. 726 (R.2721). *Examination of Foodstuffs for Contamination with Trichlorotriethylamine, Appendix to Examination of Foodstuffs for War Gases*, November 23, 1942.
62. Ptn. 1751 (V.944). *Note on the Estimation of H by Pyridine*, January 3, 1945.
63. Ptn. 1751 (V. 5310). *The Estimation of H by Reaction with DB-1*, June 13, 1945.

Research Establishment, Sutton Oak

64. S.O. R 696. *An Improved Method for the Determination of Fluorine in Aliphatic Fluoro-Compounds and Fluorophosphates*, April 28, 1944.
65. S.O. R 704. *A Physico-Chemical Study of the HBD Reaction, Part II*, February 14, 1944.

Extramural Research

66. Cambridge University (H. McCombie).
a. W.8285. *Report No. 5 on Fluorophosphates*, by H. McCombie, August 8, 1942.
b. W.12206. *Report No. 6 on Fluorophosphates and Allied Compounds*, by H. McCombie and B. C. Saunders, September 30, 1942.
c. Y.20784. *Determination of Fluorine in Organic Compounds*, by H. McCombie and B. C. Saunders, December 31, 1943.
67. Strangeways Research Laboratory, Cambridge, (H. B. Fell) V.5270. *A Note on the Estimation of Mustard Gas by the Iodoplatinate Method Using a Hilger Absorptiometer*, by H. B. Fell, June 19, 1941.
68. Imperial College, London (H. V. A. Briscoe and H. J. Emeleus).
a. W.5107. *The Quantitative Determination of Disulfur Decafluoride by the Iodometric Method*, by H. V. A. Briscoe and H. J. Emeleus, June 20, 1942.
b. Y.7333. *The Analysis of Organic Fluorine Compounds, Part II*, by H. V. A. Briscoe and H. J. Emeleus, June 7, 1943.
c. Y.16841. *The Detection of Volatile Fluorine-Containing Compounds*, by H. V. A. Briscoe and H. J. Emeleus, November 29, 1943.
d. W.20375. *Properties of Methyl Fluoroacetate (T.1302)*, by H. V. A. Briscoe and H. J. Emeleus, forwarded by the Chemical Board on February 26, 1943.

CANADIAN REPORTS

Experimental Station, Suffield, Alberta

69. Suffield Technical Minute No. 77. *Summary and Review of Present Methods of Field Sampling and Analysis for Chemical Warfare Agents*, October 23, 1944.
70. Suffield Technical Minute No. 95. *The Gutzeit Method for the Determination of Lewisite*, June 11, 1945.
71. Suffield Technical Minute No. 97. *The Use of the Evelyn Colorimeter with a Modified Iodoplatinate Method for the Determination of H*, June 13, 1945.
72. Suffield Technical Minute No. 98. *The Behavior of Compounds Related to H in Six Common Analytical Methods for the Determination of H*, June 15, 1945.

Extramural Research

73. C.P. 30., February 1943. *Use of the Evelyn Photoelectric Colorimeter in the Estimation of HS by the Iodoplatinate Method*, by R. K. Larmour and J. A. Wheat, University of Saskatchewan
74. C.P. 57., May 1944. *Estimation of H by Ortho-Tolidine*, by J. A. Wheat and R. K. Larmour, University of Saskatchewan.

AUSTRALIAN REPORTS

75. CD (Australia) Rept. No. 26. *The Sampling and Analysis of Mustard Gas Vapor under Tropical Conditions*, April 1, 1944.

76. CD (Australia) Rept. No. 54. *Estimation of Mustard by Bromine Titration*, October 9, 1944.
77. CD (Australia) Note No. 31. *A Note on the Effects of Acetone, Methanol and Diethyl Ether on the Determination of Mustard by the Iodoplatinate and Bromine Titration Methods*, October 9, 1944.
78. CD (Australia) Note No. 32. *Adaption of the β-Naphthol Method of Mustard Estimation for Routine Field Work*, October 4, 1944.
79. CD (Australia) Note No. 52. *A Comparison of Hydrogen-Ion Indication for Use in the Mercurimetric Titration of Chlorides*, May 26, 1945.

INDIAN REPORTS

80. CDRE (India) Note No. 29/43. *A Field Detector for Mustard Gas*, January 6, 1943.
81. CDRE (India) Note No. 54. *Estimation of Mustard Gas by the Gold Benzidine Method*, January 31, 1945.

Chapter 38

OSRD FORMAL REPORTS

1. OSRD 401. *Potentiometric Titration of Small Amounts of L, H, ED or DM*, by J. H. Northrop, The Rockefeller Institute for Medical Research, February 21, 1942. Div. 9-422.8-M2
2. OSRD 570. *Amplifier to Replace Galvanometer in Potentiometric Titration of Small Amounts of M-1, HS, ED or DM*, by J. H. Northrop, The Rockefeller Institute for Medical Research, May 15, 1942. Div. 9-413.1-M1
3. OSRD 880. *Photoelectric Cell for Recording the Presence of HS or Other Gases in Air*, by J. H. Northrop, The Rockefeller Institute for Medical Research, September 19, 1942. Div 9-413.3-M1
4. OSRD 1444. *Determination of HS, M-1 and Other Gases in Air, at a Distance from the Operator*, by J. H. Northrop, The Rockefeller Institute for Medical Research, May 21, 1943. Div. 9-422.8-M9
5. OSRD 3112. *Automatic Titrator for the Determination of H, L and Other Gases in Air*, by J. H. Northrop, The Rockefeller Institute for Medical Research, January 13, 1944. Div. 9-413.1-M2
6. OSRD 3419. *I. Method for the Determination of H and Thiodiglycol in Drops of Dyed Chargings. II. Determination of HN-1, HN-2, HN-3 and CG by Potentiometric Titrations. III. Cell for Potentiometric Determination of Various Gases in Air*, by J. H. Northrop, R. M. Herriott, and J. F. Gettemans, The Rockefeller Institute for Medical Research, March 29, 1944. Div. 9-415-M3
7. OSRD 3436. *Automatic Detection of Gases Which React with Silver Ions by Means of Silver Electrode*, by J. H. Northrop, The Rockefeller Institute for Medical Research, April 4, 1944. Div. 9-413.3-M2
8. OSRD 3616. *Automatic Potentiometric Recording Equipment for Determination of Chemical Warfare Agents*, by G. A. Perley and E. L. Eckfeldt, Leeds and Northrup Company, May 9, 1944. Div. 9-413.1-M3
9. OSRD 3958. *Potentiometric Titrations of HN-3 Solutions with Silver Nitrate*, by J. H. Northrop, The Rockefeller Institute for Medical Research, July 28, 1944. Div. 9-422.122-M1
10. OSRD 4218. *An Electronic Interval Timer for the Northrop Titrimeter*, by C. E. Redemann, University of Chicago Toxicity Laboratory, October 6, 1944. Div. 9-413.1-M4
11. OSRD 4308. *Apparatus for Automatic Detection of H or Other Gases Which React with Bromine by Means of the Bromine Electrode*, by J. H. Northrop, The Rockefeller Institute for Medical Research, October 31, 1944. Div. 9-422.112-M1
12. OSRD 4310. *Automatic Titrator for the Determination of H, L and Other Gases in Air. Supplement No. 4*, by J. H. Northrop and J. F. Gettemans, The Rockefeller Institute for Medical Research, October 31, 1944. Div. 9-422.8-M12
13. OSRD 4311. *Determination of HS, M-1 and Other Gases in Air at a Distance from the Operator, Supplement No. 2*, by J. H. Northrop and J. F. Gettemans, The Rockefeller Institute for Medical Research, October 31, 1944. Div. 9-422.8-M13
14. OSRD 4682. *Portable Apparatus for Rapid Estimation of H or Other Gases Which React with Bromine*, by J. H. Northrop and J. F. Gettemans, The Rockefeller Institute for Medical Research, February 10, 1945. Div. 9-422.112-M2
15. OSRD 4798. *The Estimation of Chloride by Measuring the E.M.F. of a Silver, Silver Chloride, Chloride Ion Half Cell for the Purpose of Estimating H or Other Toxics*, by J. Brockman, T. Lee, E. H. Swift, and Carl Niemann, California Institute of Technology, March 7, 1945. Div. 9-422.112-M3
16. OSRD 4839. *A Continuous Recording Meter for Determining Concentrations of H*, by L. B. Thomas, H. E. Bent, Anna Jane Harrison, and Elijah Swift, March 21, 1945. Div. 9-422.111-M1
17. OSRD 5147. *Volatile Impurities of Levinstein H*, by R. M. Herriott and J. H. Northrop, The Rockefeller Institute for Medical Research, May 29, 1945. Div. 9-212.112 M13
18. OSRD 5470. *Field Sampling of H Vapor with Tape Recorders*, by W. G. Brown, D. F. Pearson, R. J. Stell, K. E. Wilzbach, H. E. Heller, E. G. Ballweber, and R. F. Nystrom, University of Chicago, August 17, 1945. Div. 9-422.111-M2
19. OSRD 6044. *An Instrument for the Continuous Automatic Recording of H Concentrations in Air*, by A. O. Beckman, J. D. McCullough, and R. A. Crane, National Technical Laboratories, September 13, 1945. Div. 9-422.111-M3
20. OSRD 6048. *The Electrolytic Titration of H Using Polarized Platinum Indicator Electrodes*, by J. W. Sease, E. H. Swift, and Carl Niemann, California Institute of Technology, October 2, 1945. Div. 9-422.112-M4
21. OSRD 6090. *Tape Recorder Operations at the Field Experimental Station, Suffield, Alberta, Canada*, by W. G. Brown, University of Chicago, October 6, 1945. Div. 9-413.2-M3
22. OSRD 6183. *An Automatic Recording Titrimeter for Mustard*, by A. Briglio, Jr., J. Brockman, Jr., P. A. Shaffer, Jr., E. H. Swift, and Carl Niemann, California Institute of Technology, November 5, 1945. Div. 9-122.111-M4

OSRD INFORMAL REPORTS

23. Contract OEMsr-79, University of Chicago, W. G. Brown.
    a. NDRC 9.3 Inf. Rept. No. 94. *Operation of Tape Recorders for CG During Florida Trials*, by R. J. Stell, K. E. Wilzbach, and W. G. Brown, March 1, 1944. Div. 9-413.2-M1
    b. NDRC 9.3 Inf. Rept. No. 95. *Paper Tape Recording of CW Agents*, by D. E. Pearson, W. R. Remington, K. E. Wilzbach, R. J. Stell, E. G. Ballweber, N. Nicolaides and W. G. Brown, March 30, 1944. Div. 9-413.2-M2
24. Contract OEMsr-325, California Institute of Technology, E. H. Swift and Carl Niemann. Inf. Month. Prog. Rept., April 10, 1944. Div. 9-121-M1

UNITED STATES ARMY REPORTS

Chemical Warfare Service

25. DPGSR 45. *The Sampling of Mustard Vapor*, March 1, 1945. DPGSR 45, Supplement A. *The Sampling of Mustard Vapor, Supplement A, The Electrolytic Titrimeter*, July 26, 1945.
26. Med. Div. Rept. No. 28. *Titration of Acid Gases by Electrolytic Generation of Hydroxyl Ion*, April 17, 1945.
27. MIT-MR 124. *Conductimetric Determination of H Penetration*, February 22, 1945.
28. TRLR 24. *The Rate of Liberation of H and L from Some Calcareous Soils. A Preliminary Report*, March 25, 1944.
29. Med. Div. Inf. Month. Prog. Repts.
    a. January 1945.
    b. February 1945.
    c. March 1945.

UNITED STATES NAVY REPORT

Naval Research Laboratory

30. P-2208. *Chamber Tests with Human Subjects*, December 22, 1943.

BRITISH REPORTS

Chemical Defence Research Station, Porton

31. Porton Memorandum No. 19. *Chemical Sampling of Chemical Warfare Agents in Field Experiments*, October 17, 1942.
32. Porton Memorandum No. 25. *The Sampling and Analysis of Initial Clouds*, October 7, 1943.
33. Ptn. 1000 (V.35). *An Electronic Amplifier for Use with the Northrop Potentiometric Titration*, January 3, 1945.
34. Ptn. 1001/7 (U.9457). *A New Method for the Evaluation of H Vapor Concentrations in the Field, with Particular Reference to Tropical Conditions*, July 31, 1944.

CANADIAN REPORT

Experimental Station, Suffield, Alberta

35. Suffield Technical Minute No. 77. *Summary and Review of Present Methods of Field Sampling and Analysis for Chemical Warfare Agents*, October 23, 1944.

AUSTRALIAN REPORT

36. CD (Australia) Rept. No. 68. *An Apparatus for the Electrometric Titration of Mustard Gas Using Bromine Generated by Electrolysis*, March 16, 1945.

OPEN LITERATURE

37. Kolthoff, I. M. and N. H. Furman. *Potentiometric Titrations*, John Wiley and Sons, New York, 1931.
38. Longsworth, L. G. and D. A. MacInnes. *Bacterial Growth at Constant pH Quantitative Studies on the Physiology of Lactobacillus Acidophilus*, J. Bact., 31, 287-300 (1936).

Chapter 39

OSRD FORMAL REPORTS

1. OSRD 748. *A Simple Thermometric Apparatus for the Detection and Estimation of Carbon Monoxide in Air*, by J. H. Yoe and C. Lindsley, University of Virginia, July 17, 1942. Div. 9-422.7-M1
2. OSRD 848. *A Thermometric Method for the Determination of the Amount of Impregnite in Cloth*, by W. C. Johnson, University of Chicago, August 31, 1942. Div. 9-543.1-M1
3. OSRD 944. *Analysis and Treatment of Water*, by A. M. Buswell, University of Illinois, October 9, 1942. Div. 9-561-M1
4. OSRD 990. *Quantitative Determination of Anti-Vesicants in Cloths*, by A. M. Buswell, University of Illinois, November 2, 1942. Div. 9-541.22-M3
5. OSRD 1045. *Volatility of Certain Arsenic and Nitrogen Compounds*, by H. E. Bent, University of Missouri, November 10, 1942. Div. 9-200-M4
6. OSRD 1050. *The Vapor Pressure of HS and Diphenylether and Solutions of These Compounds*, by H. E. Bent, University of Missouri, November 30, 1942. Div. 9-212.112-M6
7. OSRD 1062. *Volatility of Lewinstein Mustard*, by H. E. Bent, University of Missouri, November 10, 1942. Div. 9-212.112-M5
8. OSRD 1583. *The Detection of Certain Arsenical Agents in Water, by Means of Dibiphenylthiocarbazone*, by C. C. Price and A. M. Buswell, University of Illinois, July 10, 1943. Div. 9-422.21-M3
9. OSRD 1743. *A Continuous Thermometric Apparatus for Carbon Monoxide Detection*, by J. H. Yoe and C. Lindsley, University of Virginia, August 30, 1943. Div. 9-422.7-M5
10. OSRD 1767. *A Photoelectric Instrument for the Colorimetric Detection and Determination of Carbon Monoxide*, by J. H. Yoe, J. W. Cole, and C. Lindsley, University of Virginia, September 10, 1943. Div. 9-422.7-M6
11. OSRD 1885. *The Development of a Spectrophotometric Carbon Monoxide Indicating Instrument Using Hemoglobin*, by Linus C. Pauling, California Institute of Technology, June 30, 1943. Div. 9-422.7-M4
12. OSRD 1958. *Carbon Monoxide Indicators of the Impregnated Silica Gel Type*, by J. H. Yoe, J. W. Cole, and J. M. Salsbury, University of Virginia, October 25, 1943. Div. 9-422.7-M7

13. OSRD 1959. *Studies in Carbon Monoxide Detection*, by J. H. Yoe, J. W. Cole, and J. M. Salsbury, University of Virginia, November 1, 1943. Div. 9-422.7-M8
14. OSRD 3410. *Acidimetric and Iodometric Methods for Analysis of Carbon Monoxide in Air*, by J. H. Yoe and C. Lindsley, University of Virginia, March 27, 1944. Div. 9-422.7-M9
15. OSRD 3589. *The Effect of Certain Chemical Warfare Agents in Water on Aquatic Organisms*, by A. M. Buswell, C. C. Price, C. L. Prosser, G. W. Bennett, Bruno von Limbach, and Marian James, University of Illinois, May 3, 1944. Div. 9-381-M1
16. OSRD 3621. *Treatment of Water Contaminated with Chemical Warfare Agents*, by A. M. Buswell, C. C. Price, A. C. Wiese, H. E. Hudson, and R. C. Gore, University of Illinois, May 13, 1944. Div. 9-561-M4
17. OSRD 3622. *A Thermometric Instrument for the Determination of the Amount of Impregnite in Cloth*, by G. A. Perley, Leeds and Northrup Company, May 11, 1944. Div. 9-543.1-M2
18. OSRD 3660. *The Chemistry of Three Nitrogen Mustards as Water Contaminants*, by A. M. Buswell and C. C. Price, University of Illinois, May 24, 1944. Div. 9-221.1-M12
19. OSRD 3829. *A Pellet DBT Test for Lewisite and Similar Arsenical CW Agents in Water*, by C. C. Price, B. H. Velzen, and W. G. Jackson, University of Illinois, June 26, 1944. Div. 9-422.21-M5
20. OSRD 3833. *Detection of Chemical Warfare Agents in Water and Methods for Their Removal*, by M. C. Schwartz, F. L. Goyle, J. A. Luker, E. L. Snyder, and W. B. Gurney, Louisiana State University, June 29, 1944. Div. 9-422-M2
21. OSRD 3979. *Quantitative Methods for the Determination of Certain CW Agents in Water*, by A. M. Buswell, C. C. Price, and A. C. Wiese, University of Illinois, July 19, 1944. Div. 9-422.8-M11
22. OSRD 4111. *Development of a Direct-Indicating Carbon Monoxide Instrument*, by G. A. Perley and R. H. Cherry, Leeds and Northrup Company, September 8, 1944. Div. 9-422.7-M10
23. OSRD 4193. *The Chemistry of Certain Arsenical Chemical Warfare Agents as Water Contaminants*, by A. M. Buswell, C. C. Price, R. M. Roberts, C. W. Smith, and B. H. Velzen, University of Illinois, June 26, 1944. Div. 9-213-M6
24. OSRD 4273. *A Summary of the Vapor Pressures and Volatilities of Compounds Studied at the University of Chicago Toxicity Laboratory*, by C. E. Redemann, S. W. Chaikin, R. B. Fearing, D. Van Hoesen, J. Savit, D. Benedict, and G. J. Rotariu, University of Chicago Toxicity Laboratory, November 4, 1944. Div. 9-200-M8
25. OSRD 4287. *Some Aspects of the Behavior of CC as a Water Contaminant*, by C. C. Price, T. E. Larson, K. M. Beck, F. C. Harrington, L. C. Smith, and Ilya Stephanoff, University of Illinois, October 26, 1944. Div. 9-223.1-M5
26. OSRD 4301. *Evaluation of Powdered Activated Carbons for the Purification of Military Water Supplies Contaminated with Chemical Warfare Agents*, by M. M. Benideeh, Case School of Applied Science, November 2, 1944. Div. 9-561-M5
27. OSRD 4385. *Electron Diffraction Studies on the Molecular Structure of Chemical Warfare Agents*, by Linus Pauling, California Institute of Technology, November 25, 1944. Div. 9-200-M9
28. OSRD 4676. *Equilibria in Aqueous Chloramine-T Solutions*, by C. C. Price, T. E. Phipps, and Marvin Den Harder, University of Illinois, January 31, 1945. Div. 9-411.4-M6
29. OSRD 4936. *The Quantitative Analysis for CK in Water by the DB-3 Procedure*, by C. C. Price and A. C. Wiese, University of Illinois, March 20, 1945. Div. 9-422.41-M1
30. OSRD 4989. *The Concentration of the Chlorous Principle of Water-Washed Levinstein Mustard. The Preparation of 2-Chloroethyl Sulfenyl Chloride*, by C. C. Price and O. H. Bullitt, Jr., University of Illinois, April 26, 1945. Div. 9-212.112-M14
31. OSRD 5030. *Some Aspects of the Chemistry of T as a Water Contaminant*, by C. C. Price and Albert Pohland, University of Illinois, May 2, 1945. Div. 9-212.3-M3
32. OSRD 5202. *Some Aspects of the Behavior of Q as a Water Contaminant*, by C. C. Price and R. M. Roberts, University of Illinois, June 14, 1945. Div. 9-212.113-M3
33. OSRD 5345. *Chemistry of PF-3 as a Water Contaminant*, by C. C. Price and B. H. Velzen, University of Illinois, August 10, 1945. Div. 9-211.11-M3
34. OSRD 5452. *Some Aspects of the Behavior of the Fluoroacetates and Fluoroethanol as Water Contaminants*, by C. C. Price and W. G. Jackson, University of Illinois, August 17, 1945. Div. 9-252.1-M2
35. OSRD 5528. *Further Data on the Toxicity of Various CW Agents to Fish*, by C. C. Price and Bruno von Limbach, University of Illinois, August 28, 1945. Div. 9-381-M2
36. OSRD 6043. *Determination of Carbon Monoxide in Air*, by A. O. Beckman, J. D. McCullough, and R. A. Crane, September 13, 1945.

OSRD INFORMAL REPORTS

37. Contract NDCrc-132, University of Chicago Toxicity Laboratory, E. M. K. Geiling. NDRC 9:4:1 Inf. Month. Prog. Repts. on *Toxicity and Incidency of Chemical Warfare Agents.* Div. 9-125-M2
    a. No. 21, October 10, 1944.
    b. No. 22, November 10, 1944.
    c. No. 24, January 10, 1945.
38. Contract OEMsr-139, University of Virginia, J. H. Yoe. NDRC 9:3 Inf. Rept. No. 72. *Microgravimetric Method for the Determination of Carbon Monoxide*, by J. H. Yoe, J. W. Cole, C. Lindsley, and J. M. Salsbury, May 1, 1943. Div. 9-422.7-M2
39. Contract OEMsr-312, University of Missouri, H. E. Bent. NDRC 9-3-B Inf. Rept. No. 41. *Testing Impregnated Cloth with a Hot Filament Tester*, May 5, 1942. Div. 9-543.2-M1
40. Contract OEMsr-593, University of Illinois, C. C. Price.
    a. NDRC 9:3 Inf. Rept. No. 65. *The Chemistry of Mustard Gases as a Water Contaminant*, by C. C. Price and O. H. Bullitt, Jr., August 21, 1943. Div. 9-212.11-M5
    b. NDRC 9:3 Inf. Rept. No. 104. *A Preliminary Evaluation of Certain Water-Denial Agents*, by C. C.

Price, R. E. Foster, and L. J. Reed, July 18, 1944. Div. 9-212.3-M2
c. Inf. Month. Prog. Rept., July 10, 1944.
d. Inf. Month. Prog. Rept., August 10, 1944.

UNITED STATES ARMY REPORTS

Chemical Warfare Service

41. Med. Div. Rept. No. 6. *The Detection of Organic Fluorine Compounds in Water*, October 31, 1944.
42. MD(EA) Report No. 77. *Further Data on the Contamination of Water with Compound 1130*, January 10, 1943.
43. Med. Div. Rept. No. 7. *Field Testing of Spot Test Procedure for Detection of Fluoro-Organic Compounds in Water*, March 8, 1945.
44. MRI(EA) Rept. No. 10. *The Microdetermination of HN-3 in Water*, January 21, 1944.
45. MRI(EA) Rept. No. 29. *Field Tests on Water Supplies Exposed to the Action of H*, June 7, 1944.
46. TDMR 630. *An Evaluation of Indicator Test Kits for Estimating Impregnate Content of Clothing for Use in the Field*, June 15, 1943.
47. TDMR 700. *CC No. 2 Test Kit for Impregnated Clothing: A Method for Estimating the Protective Value of Impregnated Clothing*, January 13, 1944.
48. Medical Research Laboratory (Edgewood Arsenal). Inf. Month. Prog. Repts.
    a. September 15, 1943.
    b. November 15, 1943.
    c. January 15, 1944.
    d. March 15, 1944.
49. Medical Division. Inf. Month. Prog. Repts.
    a. October 15, 1944.
    b. December 15, 1944.

UNITED STATES NAVY REPORTS

Naval Research Laboratory

50. (No number given). *Protective Clothing*, August 31, 1942.
51. P-1933. *A Survey of Proposed Methods for Rapid Evaluation of Protective Capacity of Impregnated Clothing*, September 5, 1942.
52. NRL Letter C-877-2. *Evaluation of CWS Kits for Field Determination of the Protective Value of Impregnated Clothing*, April 1, 1943

BRITISH REPORTS

Chemical Defence Research Station, Porton

53. Porton Report No. 995. *Vapour Pressure of H*, March 28, 1931.
54. Ptn. 2465 (T.4357). *Thermometric Test for the Impregnite Content of Cloth*, April 5, 1944.
55. Ptn. 3650 (T.15079). *Contamination of Water Supplies Special Water Contaminants*, January 20, 1944.
56. Ptn. 4282 (T.5945). *Methyl Fluoroacetate (T.1502) and Its Analogues as Water Contaminants*, May 6, 1943.

Extramural Research

57. University College, Southampton (N. K. Adam)
    a. *I. Vapour Pressure of Mustard*, by K. G. Denbigh and E. W. Balson, December 5, 1940.
    b. *A Redetermination of the Vapor Pressure of Mustard Gas*, by N. K. Adam, E. W. Balson and K. G. Denbigh, March 20, 1941.
    c. *Vapour Pressure of CW Agents (Lewisite)*, by N. K. Adam and E. W. Balson, February 1942.
    d. *Vapor Pressure of T.773*, by N. K. Adam and E. W. Balson, September 28, 1944.

CANADIAN REPORT

58. Chemical Warfare Laboratories Advisory Committee Report of 31st Meeting Held on May 25, 1945.

OPEN LITERATURE

59. Jacobs, M. B. *Analytical Chemistry of Industrial Poisons, Hazards and Solvents*, Interscience Publisher Inc., New York, 1941.

Chapter 40

OSRD FORMAL REPORTS

1. OSRD 66. *Preparation of Various Organic Compounds for a Study of Films, especially for Lubrication Problems*, by Roger Adams, Homer Adkins, and C. S. Marvel, Universities of Illinois and Wisconsin, January 17, 1941. Div. 9-810-M1
2. OSRD 151. *Preparation of Certain Organic Compounds for the Naval Research Laboratory*, by C. R. Noller, Stanford University, October 17, 1941. Div. 9-810-M2
3. OSRD 157. *Preparation of Compounds Requested by the Naval Research Laboratory*, by Homer Adkins, University of Wisconsin, October 20, 1941. Div. 9-831-M1
4. OSRD 163. *The Synthesis of Hydrocarbons*, by Lee I. Smith, University of Minnesota, October 20, 1941. Div. 9-810-M3
5. OSRD 186. *Preparation of Compounds Requested by the Naval Research Laboratory*, by Roger Adams and C. S. Marvel, University of Illinois, December 4, 1941. Div. 9-810-M4
6. OSRD 752. *The Preparation of Some High Molecular Weight Esters*, by Roger Adams and C. S. Marvel, University of Illinois, and M. L. Wolfrom, Ohio State University, July 20, 1942. Div. 9-810-M5
7. OSRD 1023. *Fluorocarbons*, by W. T. Miller, Cornell University, and A. L. Henne, Ohio State University, October 14, 1942. Div. 9-232-M1
8. OSRD 1792. *Fluorocarbons and Related Compounds*, by Albert L. Henne, Ohio State University, September 10, 1943. Div. 9-232-M2
9. OSRD 3163. *Aromatic Fluorocarbons*, by Frank H. Reed and Glenn C. Finger, Illinois State Geological Survey, January 19, 1944. Div. 9-232-M3
10. OSRD 3560. *Fluorocarbons*, by William T. Miller, Cornell University, May 10, 1944. Div. 9-232-M4

11. OSRD 3998. *Fluorocarbons*, by Robert D. Fowler and William B. Burford, III, Johns Hopkins University, July 17, 1941. Div. 9-232-M5
12. OSRD 4199. *An Electrolytic Cell Designed for Fluorine Productions*, by J. H. Simons, Pennsylvania State College, July 24, 1942. Div. 9-252-M1

UNITED STATES NAVY REPORTS

Naval Research Laboratory

13. P-2165. *The Laboratory Evaluation of Hydraulic Oils. I. Methods for Inflammability Test*, September 28, 1943.
14. P-2206. *Oleophobic Films Adsorbed from Oil Solutions*, November 1943.
15. P-2308. *The Laboratory Evaluation of Hydraulic Oils. II. New Fluids having Improved Inflammability Characteristics*, September 1944.
16. P-2474. *Anti-Rust Additives for Lubricating, Power Transmission and Protective Oils*, February 1945.

OPEN LITERATURE

17. Ruff, Otto, and Keim, Rudolf, *Die Reaktionsprodukte der verschiedenen Kohlenarten mit Fluor: I. Das Kohlenstoff-4-fluorid (Tetrafluormethan)*. Z. anorg. allgem. chem., 192, 249-256 (1930).
18. Simons, J. H., and Block, J. P., *Fluorocarbons. The Reaction of Fluorine with Carbon*, J. Am. Chem. Soc., 61, 2962-2966 (1939).
19. Bockemüller, W., *Organische Fluorverbindungen*, Verlag von Ferdinand Enke in Stuttgart, 1936.
20. Henne, A. L., in Gilman, Henry, *Organic Chemistry*, Second Edition, Volume I, p. 944, John Wiley and Sons, 1943.
21. Schiemann, G., *Das Borfluoriderfahren zur Darstellung Aromatischer Fluorverbindungen*. J. prakt. chem., 140, 97-116 (1934).

Chapter 41

OSRD FORMAL REPORTS

1. OSRD 4857. *Fuels for Propulsion Devices — The Synthesis of Gas-Generating Compounds*, by P. R. Austin, C. J. Mighton, F. C. McGrew, E. C. Coyner, N. B. Daly, R. V. Lindsey, and M. L. Ward, Chemical Department, E. I. duPont de Nemours and Company, March 26, 1945. Div. 9-831-M2
2. OSRD 4886. *Special Fuels for Propulsion — Evaluation of Candidates*, by P. R. Austin, C. J. Mighton, F. C. McGrew, E. C. Coyner, N. B. Daly, R. V. Lindsey, and M. L. Ward, Chemical Department, E. I. duPont de Nemours and Company, April 2, 1945. Div. 9-831-M3
3. OSRD 5022. *Special Fuels for Propulsion*, by P. R. Austin, C. J. Mighton, E. C. Coyner, N. B. Daly, R. V. Lindsey, and M. L. Ward, Chemical Department, E. I. duPont de Nemours and Company, October 1, 1945. Div. 9-831-M4
4. OSRD 5023. *Special Fuels for Propulsion*, by P. R. Austin, C. J. Mighton, E. C. Coyner, N. B. Daly, R. V. Lindsey, and M. L. Ward, Chemical Department, E. I. duPont de Nemours and Company, October 2, 1945. Div. 9-831-M4
5. OSRD 5024. *Special Fuels for Propulsion*, by P. R. Austin, C. J. Mighton, E. C. Coyner, N. B. Daly, R. V. Lindsey, and M. L. Ward, Chemical Department, E. I. duPont de Nemours and Company, October 25, 1945. Div. 9-831-M4
6. OSRD 6067. *The Preparation of Hydrogen Peroxide through the Cyclic Reduction and Oxidation of 2-Ethylanthraquinone*, by Homer Adkins, James Carnahan, and Harry Schultz, University of Wisconsin, November 20, 1945. Div. 9-253-M1
7. OSRD 6207. *Special Fuels for Propulsion*, by P. R. Austin, C. J. Mighton, E. C. Coyner, N. B. Daly, R. V. Lindsey, F. C. McGrew, and M. L. Ward, Chemical Department, E. I. duPont de Nemours and Company, November 1, 1945. Div. 9-831-M5
8. OSRD 6219. *Thermochemical Measurements on Propulsion Fuels*, by Gebhard Stegeman, University of Pittsburgh, November 10, 1945 Div. 9-831-M6

OSRD INFORMAL REPORTS

9. Contract OEMsr-945, New York University Group of the Applied Mathematics Panel, R. Courant. *Theoretical Studies Concerning the Hydropulse*, AMP Report 137.1R, by J. J. Stoker, M. Shiffman, D. C. Spencer, B. Friedman, E. Bromberg, and E. Isaacson, July 1945. Div. 9-832-M2
10. Contract OEMsr-1443, Rensselaer Polytechnic Institute, Neil P. Bailey, and H. A. Wilson. *The Hydropulse Motor*, June 1945. Div. 9-832-M1

UNITED STATES ARMY REPORTS

Signal Corps

11. Signal Corps, Aircraft Radio Branch Contract, *Report LTD 44-27, Manufacture of Sodium Borohydride*, March 21, 1944, and *Report LTD 44-46, Preparation of Sodium Borohydride on a Pilot Plant Scale*, July 19, 1944, by the Ethyl Corporation Chemical Research Laboratory.

UNITED STATES NAVY REPORTS

Naval Bureau of Aeronautics

12. Naval Bureau of Aeronautics Contract, *The Hydrolaut Thrust Generator* (R-10), by the Aerojet Engineering Corporation, January 17, 1944.
13. Naval Bureau of Aeronautics Contract NO a(s)-3855, *The Solution of the Differential Equation for the Hydropulse* (R-43), by the Aerojet Engineering Corporation, October 11, 1944.
14. Naval Bureau of Aeronautics Contract NO a(s)-3744, *Report No. 1 on Lithium Borohydride and Diborane*, by Lithalloys Corporation, October 16, 1944.
15. Naval Bureau of Aeronautics Project TED No. EES 3401, *Jet Propulsion Note No. 19, A Preliminary Study of the Hydropulse*, by Leonard B. Edelman, May 1, 1945.
16. Naval Bureau of Aeronautics Contract NO a(s) 5330, *Task No. 2, Research and Development on the Aeropulse*

and Other Self-Contained Propellant Jet Propulsion Devices (R-54), by the Aerojet Engineering Corporation, September 20, 1945.

17. Naval Bureau of Aeronautics Contract NO a(s) 5350, *Task No. 3, Research and Development on the Hydropulse and Related Jet Propulsion Devices, Semi-Annual Report* (R-55), by the Aerojet Engineering Corporation, September 20, 1945.

Naval Research Laboratory

18. Naval Research Laboratory Contract No. R-173 a-9058, *Final Report*, by H. I. Schlesinger, University of Chicago, July 1, 1945.
19. P-2571. *An Investigation of Methods for the Preparation of Diborane*, July 16, 1945.

BRITISH REPORT

Admiralty Research Laboratory

20. A.R.L. R.1/11.30 Paper P.34. *The Possibilities of the Water Jet Pulsometer in Torpedo Propulsion*, July 14, 1938.

OPEN LITERATURE

21. Schlesinger, H. I., Sanderson, R. T., and Burg, A. B. *Metallo Borohydrides. I. Aluminum Borohydride*. J. Am. Chem. Soc., **62**, 3421 (1940).
22. Schlesinger, H. I. and Brown, H. C. *Metallo Borohydrides, III. Lithium Borohydride*. J. Am. Chem. Soc., **62**, 3429 (1940).
23. Pfleiderer and Riedl, U. S. Patent 2,215,883, September 24, 1940, and U. S. Patent 2,360,012, February 20, 1945.

Chapter 12

OSRD FORMAL REPORTS

1. OSRD 4701. *The Composition of a Sample of Technical DDT from the duPont Company*, by Paul D. Bartlett, George P. Mueller, and Abraham Schneider, Harvard University, February 15, 1945. Div. 9-712.11-M1
2. OSRD 4702. *The Composition of a Sample of Technical DDT from Merck & Company, Inc.*, by Nathan L. Drake, Glen W. Kilmer, and Charles M. Baker, University of Maryland, February 15, 1945. Div. 9-712.11-M3
3. OSRD 4703. *The Composition of DDT "By-Product Oils" from Hercules Powder Company*, by Melvin S. Newman, Barney Magerlein, and William Wheatley, Ohio State University, February 15, 1945. Div. 9-712.11-M2
4. OSRD 4782. *Ultraviolet Absorption Studies on DDT*, by Weldon G. Brown and Edith M. Bokelmeck, University of Chicago, March 6, 1945. Div. 9-712.11-M4
5. OSRD 5285. *Preparation of Candidate Insect Repellents*, by Lee Irvin Smith, C. F. Koelsch, and Vaughn Engelhardt, University of Minnesota, June 30, 1945. Div. 9-711-M1
6. OSRD 5390. *Ultraviolet Absorption Spectra of Compounds Related to DDT*, by Edith M. Bokelmeck and Weldon G. Brown, University of Chicago, July 27, 1945. Div. 9-712.11-M5
7. OSRD 6054. *Preparation of Sodium Fluoroacetate, Compound 1080*, by R. L. Jenkins, E. E. Hardy, and W. B. Reed, Monsanto Chemical Company, October 15, 1945. Div. 9-721.1-M1
8. OSRD 6061. *Estimation of Small Quantities of DDT by the Phosgene Method*, by Weldon G. Brown, K. E. Wilzbach, and E. G. Ballweber, University of Chicago, October 6, 1945. Div. 9-712.13-M4
9. OSRD 6208. *DDT Formulations — Spreading Agents for Larvicidal Oils on Water*, by P. L. Salzberg, G. D. Patterson, W. V. Freed, and I. F. Walker, E. I. duPont de Nemours and Company, October 23, 1945. Div. 9-712.12-M1
10. OSRD 6226. *DDT Formulations — Solvents of High Solution Capacity*, by P. L. Salzberg, G. D. Patterson, and W. V. Freed, E. I. duPont de Nemours and Company, November 28, 1945. Div. 9-712.12-M2
11. OSRD 6334. *DDT Formulations — Water Dispersible Powders*, by P. L. Salzberg, G. D. Patterson, and I. F. Walker, E. I. duPont de Nemours and Company, February 20, 1946. Div. 9-712.12-M5
12. OSRD 6335. *DDT Formulations — Water-Dispersible Pastes*, by P. L. Salzberg, G. D. Patterson, and I. F. Walker, E. I. duPont de Nemours and Company, January 11, 1946. Div. 9-712.12-M4
13. OSRD 6336. *DDT Formulations — Surface-Active Agents for Emulsifiable DDT Concentrates*, by P. L. Salzberg, G. D. Patterson, and W. V. Freed, E. I. duPont de Nemours and Company, November 29, 1945.
14. OSRD 6337. *DDT Formulations — Applications of Infrared Spectroscopy to DDT*, by P. L. Salzberg, G. D. Patterson, J. R. Downing, W. V. Freed, and I. F. Walker, E. I. duPont de Nemours and Company, January 24, 1946. Div. 9-712.11-M7
15. OSRD 6338. *Mitigation — Fixation on Cotton Fabric*, by P. L. Salzberg, G. D. Patterson, W. V. Freed, and I. F. Walker, E. I. duPont de Nemours and Company, January 29, 1946. Div. 9-713-M2
16. OSRD 6339. *Emulsifiable Concentrates for Fly and Odor Control*, by P. L. Salzberg, G. D. Patterson, W. V. Freed, and I. F. Walker, E. I. duPont de Nemours and Company, December 17, 1945. Div. 9-712.2-M2
17. OSRD 6367. *The Preparation of Some Organic Compounds for Testing as Insect Repellents*, by Paul D. Bartlett, Hyp J. Dauben, Jr., George S. Hammond, Blaine C. McKusick, George P. Mueller, C. Kyle Parker, Sidney D. Ross, Abraham Schneider, Samuel Siegel, and G. Forrest Woods, Harvard University, December 17, 1945. Div. 9-711-M4
18. OSRD 6368. *The Synthesis of Some Compounds for Testing as Insect Repellents*, by C. D. Henton, L. Kaplan, and C. R. Noller, Stanford University, December 3, 1945. Div. 9-711-M2
19. OSRD 6369. *The Preparation of Some Compounds for Testing as Insect Repellents*, by Melvin S. Newman, Barney Magerlein, William Wheatley, and Lorence Rapoport, Ohio State University, December 28, 1945. Div. 9-711-M3

20. OSRD 6370. *The Preparation of Some Compounds for Testing as Insect Repellents*, by Nathan L. Drake, Charles M. Eaker, Glen W. Kilmer, Sidney Melamed, Wilbur J. Shenk, and Warren E. Weaver, University of Maryland, December 14, 1945. Div. 9-711-M3

21. OSRD 6371. *Some Compounds Submitted for Testing as Insect Repellents*, by Homer Adkins, Arthur C. Cope, R. C. Fuson, C. F. Koelsch, R. L. Shriner, Lee Irvin Smith, and A. L. Wilds, February 26, 1946. Div. 9-711-M6

22. OSRD 6433. *An Investigation of Procedures of Possible Value for the Chemical Estimation of the Toxic Principle of Red Squill*, by L. Kaplan, C. D. Henton, and C. R. Noller, Stanford University, December 20, 1945. Div. 9-721-M3

OSRD INFORMAL REPORTS

23. Contract OEMsr-85, University of Nebraska, C. S. Hamilton. Inf. Month. Prog. Rept., August 10, 1945. Div. 9-600-M6

24. Contract OEMsr-135, Northwestern University, C. D. Hurd. Inf. Month. Prog. Rept., August 10, 1945. Div. 9-123-M1

25. Contract OEMsr-312, University of Missouri, Henry E. Bent. *Detection for DDT*, January 5, 1945. Div. 9-712 13-M2

26. Contract OEMsr-312, University of Missouri, Henry E. Bent, Lloyd B. Thomas, and Elijah Swift, Jr. Inf. Month. Prog. Repts. Div. 9-127-M1
    a. January 10, 1945.
    b. February 10, 1945.
    c. February 28, 1945.

27. Contracts OEMemr-M-2706 and 4328, Federal Security Agency, Food and Drug Administration, Division of Pharmacology, Herbert O. Calvery and John H. Draize. Final Report, *Toxicity of Insect Repellents and Insecticides*, October 31, 1945. Div. 9-712.2-M1

28. Contract OEMemr-M-4331, United States Department of Agriculture, Agricultural Research Administration, Bureau of Entomology and Plant Quarantine. Final Report, Section 2 (of 4 sections), *Investigations on the Control of Insects and other Anthropods of Importance to the Armed Forces Conducted by Division of Insecticide Investigations, Beltsville, Maryland*, October 31, 1945.

29. Contracts OEMemr-M-4331 and 6233, the United States Department of Agriculture, Agricultural Research Administration, Bureau of Entomology and Plant Quarantine. Final Report, Section 1 (of 4 Sections), *Investigations on the Control of Insects and Other Anthropods of Importance to the Armed Forces Conducted by the Orlando, Fla., Research Laboratory*, April 1942 to October 1945. Div. 9-712.11-M6

MISCELLANEOUS

30. *Memorandum on Animal Poisons*, by Birdsey Renshaw to W. R. Kirner for transmission to R. Treichler, Fish and Wildlife Service, December 30, 1943. Div. 9-721-M1

National Research Council Insect Control Committee Report

31. *A Summary of Field Reports on 1080 (Sodium Fluoroacetate)*, by Richard A. Ormsbee, National Research Council Insect Control Committee, December 17, 1945. Div. 9-721.1-M2

UNITED STATES ARMY REPORTS

32. TDMR 1177. *A Water Dispersible DDT Suspension Concentrate (Cream or Paste)*, December 4, 1946.

33. Contract W-49-057-CWS-23, University of Chicago Toxicity Laboratory. Special Rept. on *The Toxicity to White Rats of Red Squill Powder and Various Fractions Isolated from it*, December 15, 1945.

UNITED STATES NAVY REPORTS

34. Naval Medical Research Institute, National Naval Medical Center, Bethesda, Maryland. Research Project X-168.
    a. Report No. 3, May 7, 1945.
    b. Report No. 8, September 25, 1945.

INDIAN REPORT

35. India Command, No. 1 Anti-Gas Laboratory, R. E. Report No. 67, *DDT-Identification Tests*, by F. E. Charleton, March 20, 1945.

OPEN LITERATURE

36. Haller, H. L., Paul D. Bartlett, Nathan L. Drake, Melvin S. Newman, Stanley J. Cristol, Charles M. Eaker, Robert A. Hayes, Glen W. Kilmer, Barney Magerlein, George P. Mueller, Abraham Schneider, and William Wheatley, *The Chemical Composition of Technical DDT*. J. Am. Chem. Soc., **67**, 1591 (1945).

37. Cristol, Stanley J., Robert A. Hayes, and H. L. Haller. *Determination of 1-Trichloro-2,2-bis-(p-chlorophenyl)ethane in Technical DDT*. Ind. Eng. Chem. Anal. Ed., **17**, 470 (1945).

38. Schechter, Milton S., S. B. Soloway, Robert A. Hayes, and H. L. Haller, *Colorimetric Determination of DDT*. Ind. Eng. Chem. Anal. Ed., **17**, 704 (1945).

39. Cristol, Stanley J. and H. L. Haller, *The Chemistry of DDT — A Review*. Chem. and Eng. News Ed., **23**, 2070 (1945).

40. Stoll, A., J. Renz, and A. Helfenstein. *Über die Struktur des Scillirosids*. Helv. Chim. Acta., **26**, 648 (1943).

41. Streiff, Antom J. and Frederick D. Rossini. *Method for Determining Individual Hydrocarbons in Mixtures of Hydrocarbons by Measurement of Freezing Points*. J. Research Natl. Bur. Standards, **32**, 185 (1944).

Chapter 43

OSRD FORMAL REPORTS

1. OSRD 6424. *Preparation of Antimalarial Intermediates*, by George H. Coleman, State University of Iowa, December 19, 1945. Div 9-600-M7

2. OSRD 6357. *Syntheses of Benzoquinoline Derivatives and Certain Antimalarial Intermediates*, by C. S. Hamilton, R. F. Coles, B. Ehpern, R. E. Foster, and R. D. Lipscomb, University of Nebraska, November 29, 1945. Div. 9-600-M6

3. OSRD 5466. *The Synthesis of Substituted Isoquinolines as Antimalarial Intermediates*, by R. L. Shriner and J. C. Speck, Jr., Indiana University, August 21, 1945. Div. 9-600-M5

OSRD INFORMAL REPORTS

4. Contract OEMsr-85, University of Nebraska, C. S. Hamilton. Inf. Month. Prog. Repts. Div. 9-128-M1
   a. July 8, 1944.
   b. August 8, 1944.
   c. September 8, 1944.
   d. October 7, 1944.
   e. November 10, 1944.
   f. December 9, 1944.
   g. January 10, 1945.
   h. February 10, 1945.
   i. March 10, 1945.
   j. April 10, 1945.
   k. May 10, 1945.
   l. June 10, 1945.
   m. July 10, 1945.
   n. August 10, 1945.

5. Contract OEMsr-97, Iowa State College, Henry Gilman. Inf. Month. Prog. Repts. Div. 9-122-M3
   a. September 10, 1944.
   b. October 10, 1944.
   c. November 10, 1944.
   d. December 10, 1944.
   e. January 10, 1945.
   f. February 10, 1945.
   g. March 10, 1945.
   h. April 10, 1945.
   i. May 10, 1945.
   j. June 10, 1945.
   k. July 10, 1945.
   l. August 10, 1945.

6. Contract OEMsr-135, Northwestern University, C. D. Hurd. Inf. Month. Prog. Repts. Div. 9-123-M1
   a. July 10, 1944.
   b. August 10, 1944.
   c. September 6, 1944.
   d. October 6, 1944.
   e. November 10, 1944.
   f. December 9, 1944.
   g. January 10, 1945.
   h. January 29, 1945.
   i. March 8, 1945.
   j. April 9, 1945.
   k. May 10, 1945.
   l. June 8, 1945.
   m. July 10, 1945.
   n. August 10, 1945.

7. Contract OEMsr-195, Indiana University, R. L. Shriner. Inf. Month. Prog. Repts. Div. 9-300-M3
   a. January 10, 1945.
   b. February 10, 1945.
   c. March 10, 1945.
   d. April 10, 1945.
   e. May 10, 1945.
   f. June 10, 1945.

8. Contract OEMsr-223, State University of Iowa, George Coleman. Inf. Month. Prog. Repts. Div. 9-600-M2
   a. September 10, 1944.
   b. October 10, 1944.
   c. November 10, 1944.
   d. December 10, 1944.
   e. January 10, 1945.
   f. February 10, 1945.
   g. March 10, 1945.
   h. April 10, 1945.
   i. May 10, 1945.
   j. June 10, 1945.
   k. July 10, 1945.
   l. August 10, 1945.

9. Contract OEMsr-309, University of Illinois, R. C. Fuson. Inf. Month. Prog. Repts. Div. 9-126-M1 Div. 9-255-M9 Div. 9-600-M4
   a. September 10, 1944.
   b. October 10, 1944.
   c. November 10, 1944.
   d. December 10, 1944.
   e. January 10, 1945.
   f. February 10, 1945.
   g. March 10, 1945.
   h. April 10, 1945.
   i. May 10, 1945.
   j. June 10, 1945.
   k. July 10, 1945.
   l. August 10, 1945.

10. Contract OEMsr-304, University of Wisconsin, Homer Adkins, and A. L. Wilds. Inf. Month. Prog. Repts. Div. 9-200-M11 Div. 9-600-M2
   a. September 9, 1944.
   b. October 10, 1944.
   c. November 10, 1944.
   d. December 10, 1944.
   e. January 10, 1945.
   f. February 10, 1945.
   g. March 10, 1945.
   h. April 10, 1945.
   i. May 10, 1945.
   j. June 11, 1945.
   k. July 10, 1945.
   l. August 10, 1945.

11. Contract OEMsr-363. Final Rept. on *Preparation of Intermediates and Synthesis of Potential Antimalarials*, by Charles D. Hurd, Otis E. Fancher, William A. Bonner, and Rex J. Sims, Northwestern University, January 31, 1946. Div. 9-600-M10

12. Contract OEMsr-364. Final Rept. on *Synthesis of Antimalarial Intermediates*, by George H. Coleman, Stanley S. Brandt, Joseph E. Callen, Elmer E. Combs, Clinton A. Dornfeld and Ronald E. Pyle, State University of Iowa, December 31, 1945. Div. 9-600-M8

13. Contract OEMemr-505. Final Rept. on *Antimalarial Intermediates and Drugs*, by Henry Gilman, S. Avakian, R. A. Benkeser, R. N. Clark, A. E. Lindblad, F. J. Marshall, F. A. Martin, S. P. Massie, Jr., and J. E. Myers, Iowa State College, March 30, 1946.
Div. 9-600-M12

14. Contract OEMemr-506. Final Rept. on *Syntheses of Benzoquinoline Derivatives and Certain Antimalarial Intermediates*, by C. S. Hamilton, R. F. Coles, R. E. Foster, and R. D. Lipscomb, University of Nebraska, December 31, 1945. Div. 9-600-M9

15. Contract OEMemr-507. Final Rept. on *Synthesis of Potential Antimalarial Agents and Intermediates*, by Homer Adkins, Harry P. Schultz, James E. Carnahan, A. L. Wilds, Melvin Rebenstorf, and Ruther Guthker, University of Wisconsin, February 28, 1946.
Div. 9-600-M11

16. Contract OEMemr-570. Final Rept. on *The Synthesis of Candidate Antimalarial Drugs and Related Compounds*, by R. C. Fuson, C. C. Price, R. A. Bauman, D. M. Burness, E. Howard, Jr., W. E. Parham, and L. J. Reed, University of Illinois, May 31, 1946. Div. 9-600-M13

OSRD APPOINTEES

DIVISION 9

Chief

W. R. KIRNER

Technical Aide

JONATHAN W. WILLIAMS

Members

HOMER ADKINS
M. M. BRUBAKER
A. M. BUSWELL
W. S. CALCOTT
A. C. COPE
L. F. FIESER
K. FOLKERS
H. S. GASSER
C. S. HAMILTON
W. C. JOHNSON
C. S. MARVEL
C. NIEMANN
R. L. SHRINER
HOMER W. SMITH

SECTION 9-1

Chiefs

HOMER ADKINS — A. C. COPE

Technical Aides

JOSEPH DEC — E. WILKINS REEVE

JONATHAN W. WILLIAMS

SECTION 9-2

Chiefs

A. C. COPE — HOMER ADKINS

Technical Aides

JOSEPH DEC — MARSHALL GATES

SECTION 9-3

Chiefs

WARREN C. JOHNSON — CARL G. NIEMANN

Technical Aides

DONALD PEARSON — MORRIS B. JACOBS

SECTION 9-4

Chief

H. S. GASSER

Technical Aides

A. C. COPE — BIRDSEY RENSHAW

STANFORD MOORE

SECTION 9-5

Chief

HOMER W. SMITH

Technical Aides

STANFORD MOORE — BIRDSEY RENSHAW

JOHN A. ZAPP, JR.

Contract Numbers	*Contractor*	*Subject*
NDCrc–4	(See OEMsr–304)	
NDCrc–6	(See OEMsr–304)	
NDCrc–7	(See OEMsr–135)	
NDCrc–10	(See OEMsr–136)	
NDCrc–16	(See OEMsr–85)	
NDCrc–17	(See OEMsr–372)	
NDCrc–19	(See OEMsr–97)	
NDCrc–39	(See OEMsr–87)	
NDCrc–43	(See OEMsr 161)	
NDCrc–48	(See OEMsr–300)	
NDCrc–61	(See OEMsr–97)	
NDCrc–72	(See OEMsr–301)	
NDCrc–89	(See OEMsr–312)	
NDCrc–132	University of Chicago Chicago, Ill.	Studies and experimental investigations in connection with the vesicant action of certain chemical warfare materials as lung irritants; the determination of the toxicity and irritant action of all types of chemical warfare agents, and, upon request, the undertaking of further studies and experimental investigations of the preparation and properties of chemical substances for military or naval application.
NDCrc–134	(See OEMsr–70)	
NDCrc–136	Harvard University Cambridge, Mass.	Studies and experimental investigations in connection with the preparation of Lewisite and radioactive sulfur and arsenic compounds; the mechanism of the action of various decontaminants upon Lewisite and mustard gas; a search for a non-corrosive decontaminant; the inter-conversion of Lewisite isomers together with the preparation of new analogs of Lewisite; the factors affecting the field use of chemical warfare agents; the synthesis, stability, and mechanism of action of non-volatile toxic agents and other agents; insecticides and insect repellents.
NDCrc–151	Rockefeller Institute for Medical Research New York, N. Y.	Studies and experimental investigations in connection with biological methods for detection of persistent chemical agents.
NDCrc–169	Harvard University Cambridge, Mass.	Studies and experimental investigations in connection with the physiological action of mustard gas, beta halogen sulfides, and Lewisite by means of radioactive sulfur and arsenic; the determination of the course of action of chemical warfare agents through the use of radioactive tracers; the physiological mechanisms involved in the production of injury by flame thrower attack.
NDCrc–172	(See OEMsr–139)	
OEMsr–48	(See OEMsr–300)	
OEMsr–62	Rockefeller Institute for Medical Research New York, N. Y.	Studies and experimental investigations in connection with methods of immunization against the action of certain war gases.
OEMsr–78	(See OEMsr–304)	
OEMsr–79	University of Chicago Chicago, Illinois	Studies and experimental investigations in connection with methods for the detection of mustard gas and other persistent agents; the preparation of certain reagents for test purposes; the development of a complete gas detector kit; the factors affecting the field use of chemical warfare agents, and methods for detection and analysis of insecticides.
OEMsr–80	(See OEMsr–372)	
OEMsr–85	University of Nebraska Lincoln, Nebraska	Studies and experimental investigations in connection with the preparation of organic arsenicals; the preparation of certain toxic agents and the synthesis of therapeutic intermediates.
OEMsr–86	Harvard University Cambridge, Mass.	Studies and experimental investigations in connection with the range of combination of vesicants with biological materials; the physiological chemistry of the local and systemic actions of chemical warfare agents.
OEMsr–87	University of Chicago Chicago, Ill.	Studies and experimental investigations in connection with the detection of certain persistent chemical agents; development of quantitative methods of analysis of all types of war gases; colorimetric methods of

Contract Numbers	*Contractor*	*Subject*
		analysis; the improvement of detector papers; the development of detectors, primarily of the silica gel type; and all analytical procedures which should be considered for field laboratories.
OEMsr-94	(See OEMsr-532)	
OEMsr-97	Iowa State College Ames, Iowa	Studies and experimental investigations in connection with the preparation of organo-metallic compounds of possible use as weapons of war, including flame throwers; organo-cadmium, phosphorus, and chromium compounds as chemical warfare agents; organic boring derivatives and other organo-metallic compounds to affect adversely the canister ingredients; factors affecting the field use of chemical warfare agents; the preparation and properties of non-volatile toxic agents and the synthesis of therapeutic agents and intermediates.
OEMsr-109	(See OEMsr-593)	
OEMsr-114	(See OEMsr-394)	
OEMsr-123	Washington University St. Louis, Missouri	Studies and experimental investigations in connection with the effect of vesicants on the enzyme system of the skin and its relation to pathological lesions; the pharmacological effects of chemical warfare agents and their actions on enzyme systems.
OEMsr-129	Rockefeller Institute for Medical Research New York, N. Y.	Studies and experimental investigations in connection with the isolation of tissue enzymes acted on by vesicants and other aspects of vesicant-enzyme chemistry, and the investigation of methods for the detection and identification of war gases, and factors affecting the field use of chemical warfare agents.
OEMsr-134	(See OEMsr-139)	
OEMsr-135	Northwestern University Evanston, Ill.	The reaction between mustard gas and decontaminating agents, other chemistry of these decontaminating agents, and the discovery of non-corrosive decontaminants for mustard gas; the removal of the residual odor after destruction of mustard gas by weathering or by decontamination; the synthesis of certain compounds requested by the CMR and CWS; factors affecting the field use of chemical warfare agents, and the synthesis of therapeutic intermediates.
OEMsr-136	Leland Stanford Junior University Stanford University, Calif.	Studies and experimental investigations in connection with the preparation of not less than six and not more than twelve hydrocarbons used in lubrication studies, the preparation of non-arsenical and non-antimonial sternutators and unsaturated toxic agents, certain synthetic products related to V, and preparation of candidate insect repellents.
OEMsr-139	University of Virginia Charlottesville, Va.	Studies and experimental investigations in connection with the development of a test for mustard; the reactions between persistent chemical agents and certain inorganic ions; dyes for detector paint; methods for detecting extremely low concentrations of carbon monoxide; looking toward the development of a compact simple instrument for the detection of carbon monoxide at concentrations of 0.005% or less, and factors affecting the field use of chemical warfare agents.
OEMsr-144	Cornell University Medical College, New York, N. Y.	Studies and experimental investigations in connection with the combination of halogenated thioethers with proteins and other tissue constituents; to determine how mustard gas combines with proteins and nucleoproteins; to attempt to discover an immunization agent against mustard gas; a study of the biochemistry of the action of the sulfur containing vesicants.
OEMsr-150	Pennsylvania State College State College, Penna.	Studies and experimental investigations in connection with the preparation of fluorocarbons by methods involving the direct fluorination of carbon.
OEMsr-161	Ohio State University Research Foundation Columbus, Ohio	The synthesis of esters for use in investigation of lubrication, and the preparation of certain nitrogen-containing chemical warfare agents.
OEMsr-162	Ohio State University Research Foundation Columbus, Ohio	Studies and experimental investigations in connection with the preparation of fluorocarbons and a study of their properties.
OEMsr-195	Indiana University Bloomington, Indiana	Studies and experimental investigations in connection with the synthesis of compounds related to urushiol, lacool, rhengol, thitsiol and other

Contract Numbers	*Contractor*	*Subject*
		natural vesicants; the preparation of amines which dimerize to choline-like derivatives; the preparation of highly toxic agents.
OEMsr-209	Wesleyan University Middletown, Conn.	Studies and experimental investigations in connection with the synthesis of compounds related to urushiol, laccol and other natural vesicants.
OEMsr-214	(See OEMsr-532)	
OEMsr-222	(See OEMsr-304)	
OEMsr-223	State University of Iowa Iowa City, Iowa	Studies and experimental investigations in connection with the properties of nitrogen trichloride, including a study of its desensitization; preparation of various intermediates for use in the synthesis of explosives, war gases, and prophylactic agents; the preparation of various war gases, and, more particularly, a study of 1070, 1130, and their homologues; conduct a study of factors affecting the field use of chemical warfare agents.
OEMsr-237	Cornell University Ithaca, New York	Studies and experimental investigations in connection with the preparation of polyfluorinated hydrocarbons and to furnish various samples thereof for evaluation as lubricants.
OEMsr-276	(See OEMsr-593)	
OEMsr-300	University of Illinois Urbana, Illinois	Studies and experimental investigations in connection with the preparation of certain derivatives of aziline, and not less than eight and not more than fourteen substances specifically agreed upon; stabilization and storage of mustard gas; the reaction between mustard gas and decontaminating agents; preparation of a variety of chemical agents containing nitrogen, sulfur, halogen and arsenic; synthesis of therapeutic intermediates; the interpretation of data on synthetic, analytical and inorganic problems including protective agents and fabrics.
OEMsr-301	Ohio State University Research Foundation Columbus, Ohio	Studies and experimental investigations in connection with the development of test papers for persistent chemical agents; synthetic inorganic problems, and the development of procedures for the analysis of arsenicals.
OEMsr-304	University of Wisconsin Madison, Wisconsin	The preparation of a benzyl bromide derivative and not less than six and not more than twelve other compounds specifically agreed upon by the contractor and the Committee; the preparation of various synthetic compounds requested by the Armed Services; the preparation and utilization of protective and toxic agents; a study of decontamination, and the synthesis of therapeutic intermediates.
OEMsr-312	University of Missouri Columbia, Missouri	The detection and analysis of smokes
OEMsr-313	Rockefeller Institute for Medical Research New York, N. Y.	Studies and experimental investigations in connection with the action of vesicants on protein constituents and intracellular proteolytic enzymes; chemistry of the reactions of chemical warfare agents with special reference to the reactions with the functional groups characteristic of living tissues.
OEMsr-319	University of Rochester Rochester New York	Studies and preliminary investigations in connection with a method for the detection of Compound 1120; methods for the detection of chemical warfare agents and the development of new arsenical detectors suitable for use on silica gel and in papers and factors affecting the field use of chemical warfare agents.
OEMsr-325	California Institute of Technology Pasadena, Calif.	Studies and experimental investigations on a systematic analysis of chemical warfare agents, and the development of practical methods for their use; the factors affecting the field use of chemical warfare agents.
OEMsr-332	Johns Hopkins University Baltimore, Maryland	Studies and experimental investigations in connection with the preparation of fluorocarbons by methods involving the direct fluorination of carbon and the fluorination of hydrocarbons.
OEMsr-361	E. I. duPont de Nemours & Co. Wilmington, Del.	Studies and experimental investigations in connection with the retarding of deterioration in certain types of impregnated fabrics; development of permeable gas-protective fabrics.
OEMsr-371	Purdue Research Foundation Lafayette, Indiana	Studies and experimental investigations in connection with the reaction of nitrogen tetroxide with olefins.

Contract Numbers	*Contractor*	*Subject*
OEMsr-372	University of Minnesota Minneapolis, Minn.	Studies and experimental investigations in connection with hydrocarbons used in lubrication studies, etc.; the preparation of certain amido compounds for use in connection with the synthesis of new impregnites; a study of photo-oxides; the preparation of various derivatives of acrylonitrile, and the preparation of candidate insect repellents.
OEMsr-374	(See OEMsr-715)	
OEMsr-375	E. I. duPont de Nemours & Co. Wilmington, Del.	Studies and experimental investigations in connection with special fabrics for protection against chemical warfare agents.
OEMsr-377	E. I. duPont de Nemours & Co. Wilmington, Del.	Studies and experimental investigations in connection with the preparation of DTH and related compounds; preparation of BAL and related protective and therapeutic agents for war gases.
OEMsr-394	University of Chicago Chicago, Ill.	The preparation of certain nitrogen-containing chemical warfare agents and antivesicant agents; the decomposition of diphosgene into phosgene; the preparation of phosphorus and arsenic analogs of pyridine.
OEMsr-434	Rockefeller Institute for Medical Research New York, N. Y.	Studies and experimental investigations in connection with the development of an accurate method for the application of chemical warfare and therapeutic agents to the skin; the degree and the mechanism of the vesicant action of mustard and related agents, and a study of factors affecting the field use of chemical warfare agents.
OEMsr-439	Eastman Kodak Co. Rochester, N. Y.	Studies and experimental investigations in connection with the development of special fabrics for protection against chemical warfare agents.
OEMsr-456	University of California Berkeley, California	Studies and experimental investigations in connection with a radiographic evaluation of skin sections.
OEMsr-469	University of Illinois Urbana, Ill.	A study of aromatic fluorine compounds.
OEMsr-532	Johns Hopkins University Baltimore, Maryland	Studies and experimental investigations in connection with the mechanism of action of vesicants on the chemical constituents of tissues; a study of the hydrolysis of war gases in the liquid phase and of other related physical chemical properties; measurements of reaction, solubilities, and other properties bearing on the action and penetration of chemical warfare agents.
OEMsr-549	E. I. duPont de Nemours & Co. Wilmington, Del.	Studies and experimental investigations in connection with the production of chemical warfare agents from olefins and other unsaturated compounds; synthesis of chemical warfare toxic and vesicant agents.
OEMsr-556	New York University New York, N. Y.	Studies and experimental investigations in connection with the pharmacology of 1070 and allied compounds; pharmacology and pathology and factors affecting the field use of chemical warfare agents; consultation with persons eminent in their respective fields of endeavor in connection with a survey of the possibilities and the formulation of plans for furthering the progress of medicine and related sciences.
OEMsr-559	Rohm and Haas Company, Inc. 222 West Washington Square Philadelphia, Penna.	Studies and experimental investigations in connection with evaluating the efficiency of fabrics impregnated with certain materials against various chemical agents, involving both routine testing and development of new, improved methods of testing.
OEMsr-560	(See OEMsr-360)	
OEMsr-574	E. I. duPont de Nemours & Co. Wilmington, Del	Studies and experimental investigations in connection with new methods for synthesizing nitrogen-containing vesicants and of agents for affecting eyes; the preparation of various alkanolamines by procedures which do not require the use of the corresponding alkylene oxides and to make such surveys of the process as may be needed to determine the commercial feasibility of these methods.
OEMsr-575	Rohm and Haas Company, Inc. 222 West Washington Square Philadelphia, Penna.	Studies and experimental investigations in connection with research and development on permeable protective clothing containing absorbents; preparation of impregnated fabrics, particularly those impregnated by activated carbon, and to obtain suitable binders for retaining the carbon, in an activated condition, in the cloth; development and testing of permeable fabrics designed to provide protection against vesicant chemical agents.

Contract Numbers	*Contractor*	*Subject*
OEMsr-585	E. I. duPont de Nemours & Co. Wilmington, Del.	Studies and experimental investigations in connection with the decontamination of painted surfaces which have been exposed to chemical warfare agents; the development of new means for decontaminating inanimate objects which have been contaminated with chemical warfare agents, including means for decontaminating protective clothing containing activated carbon.
OEMsr-593	University of Illinois Urbana, Ill.	Studies and experimental investigations in connection with the development of methods of analysis and detection of chemical warfare agents in water and methods for their removal or neutralization; the construction and operation of a pilot plant for the purpose of determining the applicability of purification reactions under practical conditions; the development of methods for the quantitative determination of antivesicants in fabrics; the design of two types of field kits for the detection and identification of toxic agents in water supply; isolation of products of hydrolysis of toxic agents and of products obtained upon the addition of decontaminating agents; factors affecting the field use of chemical warfare agents; the synthesis of therapeutic intermediates and a study of the metabolism of antimalarials.
OEMsr-607	University of Illinois Urbana, Ill.	Studies and experimental investigations in connection with the preparation of boron compounds of possible use as chemical warfare agents; the resolution of BAL.
OEMsr-644	Commercial Solvents Corp. Terre Haute, Ind.	Studies and experimental investigations in connection with the development of processes for the production of a certain chemical compound known as S-461 and especially the installation of a pilot plant for such manufacture; the experimental operation of such pilot plant and the production of at least 10,000 pounds of S-461; a study of methods of improving such manufacture, and the development of methods for the preparation of diacetyl and related compounds including their chlorination.
OEMsr-655	E. I. duPont de Nemours & Co. Wilmington, Del.	Studies and experimental investigations in connection with processes for the production of impregnites.
OEMsr-656	E. I. duPont de Nemours & Co. Wilmington, Del.	Studies and experimental investigations in connection with the preparation of raw materials for chemical warfare agents, and more particularly a study of the preparation of arsenic trichloride using HCl as a source of chlorine, and the erection and operation of an $AsCl_3$ pilot plant using the hydrogen chloride process; the beneficiation of arsenic ores as a source of arsenic chloride; the preparation of sulphur chloride without the use of elemental chlorine; the production of thionyl chloride; the stabilization of sulphur trioxide; studies on a modified process for the preparation of $AsCl_3$ from crude As_2O_3 and sulfur monochloride; the corrosion of metals by chemical warfare agents.
OEMsr-670	Leeds and Northrup Co. 4901 Stenton Avenue Philadelphia, Penna.	Studies and experimental investigations in connection with the development of a direct-indicating carbon monoxide instrument.
OEMsr-671	Arnold O. Beckman South Pasadena, Calif.	Studies and experimental investigations in connection with the development of a carbon monoxide-indicating instrument for low concentrations of carbon monoxide in air; development of indicating instruments for determining low concentrations of noxious gases in air.
OEMsr-681	Johns Hopkins University Baltimore, Maryland	Studies and experimental investigations in connection with the preparation of "W" in various forms so that supplies will be available for test purposes.
OEMsr 699	Washington University St. Louis, Missouri	Studies and experimental investigations in connection with the extraction of natural products.
OEMsr-703	California Institute of Technology Pasadena, Calif.	Studies and experimental investigations in connection with the development of a spectrophotometric carbon monoxide-indicating instrument using hemoglobin.
OEMsr-714	Leeds and Northrup Company 4901 Stenton Avenue Philadelphia, Penna.	Studies and experimental investigations in connection with the development of model apparatus for quantitative determination of impregnites in clothing so that standardization tests can be made, and to construct a

Contract Numbers	*Contractor*	*Subject*
		sufficient number of units of a selected satisfactory model to determine reproducibility of results obtainable.
OEMsr-715	University of Maryland College Park, Maryland	Studies and experimental investigations in connection with improvements in the preparation and handling of igniters for incendiary bombs; the preparation of reagents for the detection of arsenicals, and the development of methods for the detection of fluorine-containing compounds.
OEMsr-720	Woonsocket Rayon Company Woonsocket, R. I.	Studies and experimental investigations in connection with methods for incorporating activated carbon into rayon fibres, or, more particularly, the dispersion of activated carbon in viscose prior to spinning, and related problems.
OEMsr-742	Merck & Co., Inc. Rahway, New Jersey	Studies and experimental investigations in connection with the development of processes for the production, on a pilot plant scale, of benzil and derivatives, or such compounds as are required for the preparation of impregnites; the development of a process suitable for the large scale production of chloroamide 8-330, or such compounds as are required for the preparation of impregnites.
OEMsr-750	Merck & Co., Inc. Rahway, New Jersey	Studies and experimental investigations in connection with the preparation and testing of substances to be used as neutralizing or therapeutic agents for mustard burns.
OEMsr-753	California Institute of Technology Pasadena, Calif.	Studies and experimental investigations in connection with the determination, by electron diffraction, of the molecular structure of chemical warfare agents.
OEMsr-760	E. I. duPont de Nemours & Co. Wilmington, Del.	Studies and experimental investigations in connection with the development of a process for the preparation of BAL, and to equip, install, and operate a pilot plant which will yield 20 gallons of the finished material.
OEMsr-761	E. I. duPont de Nemours & Co. Wilmington, Del.	A chemical study of certain steps involved in the synthesis of a certain chemical warfare agent; an engineering study looking toward its commercial production, and a study of its stability and storage.
OEMsr-770	Kendal Company Walpole, Mass.	Studies and experimental investigations in connection with the development of agents and methods for binding activated carbon to cloth; a study of the preparation of fabrics coated with activated carbon, and research on the evaluation of the fabrics produced.
OEMsr-813	Leeds and Northrup Philadelphia, Penna.	Studies and experimental investigations in connection with the development and construction of an automatically recording potentiometric apparatus for the determination of the amount of chemical warfare agents in air at low concentrations.
OEMsr-831	Eastman Kodak Company Rochester, N. Y.	Studies and experimental investigations in connection with the preparation of 200 pounds of E.D. by the lead tetraethyl process worked out by Kharasch.
OEMsr-835	Purdue Research Foundation Lafayette, Ind.	Studies and experimental investigations in connection with the preparation of thiodiglycol mustard.
OEMsr-842	Cornell University Ithaca, New York	Studies and experimental investigations in connection with microscopic identification of chemical warfare agents and their derivatives.
OEMsr-843	Procter & Gamble Co. Ivorydale, Ohio	Studies and experimental investigations in connection with the semi-works production of "W" and, more particularly, methods of isolating and concentrating "W" from "WB" and the ultimate preparation, if possible, of about one hundred pounds of "W"; preparation of finely divided "W", either by grinding or direct precipitation, which will be suitable for dispersion from munitions; and engineering studies on both a laboratory and pilot plant scale to render practicable the use of commercially available castor bean pomace for the production of "W" on a large scale.
OEMsr-845	Monsanto Chemical Company Phosphate Division Anniston, Alabama	A study of organic derivatives of phosphorus and preparation of five hundred pounds each of dimethyl and diisopropyl fluorophosphates, methyl fluoroacetate and fluoroethanol; conduct a study of laboratory and pilot plant procedures for the preparation of certain volatile and non-volatile chemical warfare agents.

Contract Numbers	*Contractor*	*Subject*
OEMsr-858	Merck & Co., Inc. Rahway, New Jersey	Studies and experimental investigations in connection with the preparation of 25 to 50 pounds of V.
OEMsr-867	Allied Chemical & Dye Corp. National Aniline Division New York, N. Y.	Studies and experimental investigations in connection with the nitrosation of methyl ethyl ketone and the preparation of certain specified CW agents, and the testing of the laboratory results by approximately twenty pilot plant trials.
OEMsr-884	Jos. Bancroft & Sons Co. Wilmington, Del.	Studies and experimental investigations in connection with the development of a method, for use on a plant scale, for the impregnation of fabric with activated carbon.
OEMsr-901	Columbia University New York, N. Y.	Conduct immunochemical studies.
OEMsr-910	Case School of Applied Science Cleveland, Ohio	Studies and experimental investigations in connection with the detection of chemical warfare agents in water and methods for their removal; operation of a small water plant to study the effectiveness of proposed procedures; design of two types of field kits for the detection and identification of toxic agents in water supply; isolation of products of hydrolysis of toxic agents and of products obtained upon the addition of decontaminating agents.
OEMsr-913	Shell Development Company 100 Bush Street San Francisco, Calif.	Studies and experimental investigations in connection with the development of a process for the production of diacetyl dioxide by effecting the vapor phase catalytic oxidation of methyl ethyl ketone to diacetyl in the presence of a catalyst comprising cuprous oxide, and reacting the resulting diacetyl with urea in the presence of an acid, and especially (1) the installation of a pilot plant for such studies, (2) the experimental operation of such pilot plant, and (3) a study of the methods of improving such manufacture.
OEMsr-933	E. I. duPont de Nemours & Co. Wilmington, Del.	Studies and experimental investigations in connection with the preparation of 500 pounds of ethyldichlorarsine by an improved process.
OEMsr-935	Sayles Finishing Plants, Inc. Saylesville, R. I.	Studies and experimental investigations in connection with the development of methods for producing, on a plant scale, permeable protective fabric containing activated carbon.
OEMsr-942	Louisiana State University Agricultural and Mechanics College Baton Rouge, La.	Studies and experimental investigations in connection with the detection of chemical warfare agents in water and methods for their removal.
OEMsr-1006	University of Maryland College Park, Maryland	Studies and experimental investigations in connection with the preparation of non-irritant anti-gas ointments.
OEMsr-1050	New York University New York, N. Y.	Studies and experimental investigations in connection with cellular and intracellular constituents with the object of elucidating the changes in physical chemical properties of such constituents associated with the action of chemical warfare agents; the composition and fractionation of crude W.
OEMsr-1080	E. I. duPont de Nemours & Co. Wilmington, Del.	Perform consulting work in connection with the preparation of W in a finely divided form suitable for dispersion as an aerosol and conduct laboratory tests on samples of W supplied to the Contractor for that purpose.
OEMsr-1088	E. I. duPont de Nemours & Co. Wilmington, Del.	Studies and experimental investigations in connection with the preparation of ethanesulfinic looking toward the development of an economical and practical method which will have possibilities for enlargement to full plant scale. The work is expected to involve the preparation of certain quantities of ethanesulfinic, which, it is estimated, will be 1500 to 2000 pounds.
OEMsr-1092	University of Minnesota Minneapolis, Minn.	Studies and experimental investigations in connection with the sensitivities, stabilities, and modifications of reagents in detector kits used by the Army and Navy, and new types of detectors for the kits or for other use.
OEMsr-1093	American Cyanamid Company New York, N. Y.	Studies and experimental investigations in connection with the preparation of new type chloroamides on a laboratory scale.
OEMsr-1124	Merck & Co., Inc. Rahway, New Jersey	Studies and experimental investigations in connection with the preparation of non-volatile chemical warfare agents.

Contract Numbers	*Contractor*	*Subject*
OEMsr-1157	Monsanto Chemical Company St. Louis, Missouri	Studies and experimental investigations in connection with the preparation of S-330.
OEMsr-1280	Vanderbilt University Nashville, Tenn.	Studies and experimental investigations in connection with the incorporation of toxic compounds with resins and other materials in order to improve their effectiveness as warfare agents; the preparation of toxic agents and synthesis of antimalarials and their intermediates.
OEMsr-1282	Motion Picture Engineering Corp. 2800 Cullom Street Chicago, Ill.	Prepare working drawings of the tape recorder, developed under Contract OEMsr-79 with the University of Chicago, for the recording of vapor concentrations of chemical warfare agents in the field, and produce 100 models thereof.
OEMsr-1303	University of Maryland College Park, Maryland	Studies and experimental investigations in connection with a chemical investigation of insecticides and repellents.
OEMsr-1304	Harvard University Cambridge, Mass.	Studies and experimental investigations in connection with a chemical investigation of insecticides and repellents.
OEMsr-1307	Ohio State University Research Foundation Columbus, Ohio	Studies and experimental investigations in connection with a chemical investigation of insecticides and repellents.
OEMsr-1327	American Viscose Corporation Wilmington, Del.	Studies and experimental investigations in connection with the preparation of carbon-viscose rayon yarn and the development of suitable methods of incorporating this yarn into knit and woven fabrics suitable for use by the Armed Services.
OEMsr-1360	E. I. duPont de Nemours & Co. Wilmington, Del.	Studies and experimental investigations in connection with gas generating and high energy compounds suitable for use as fuels in jet propulsion.
OEMsr-1362	E. I. duPont de Nemours & Co. Wilmington, Del.	Studies and experimental investigations in connection with formulations of DDT relating to its use as an insecticide and treatment of fabrics for control of insects.
OEMsr-1383	Remington Arms Company, Inc. Bridgeport, Conn.	Studies and experimental investigations in connection with development of devices suitable for the dispersion of non-volatile materials.
OEMsr-1464	University of Pittsburgh Pittsburgh, Pa.	Studies and experimental investigations in connection with thermochemical measurements on substances of interest as propulsion fuels.

SERVICE PROJECT NUMBERS

The projects listed below were transmitted to the Executive Secretary, NDRC, from the War or Navy Department through either the War Department Liaison Officer for NDRC or the Office of Research and Inventions (formerly the Coordinator of Research and Development), Navy Department.

Service Project Number	*Subject*
AC-59	The Development of a Carbon Monoxide Detector for Aircraft.
CWS-2	Study of the Theory of Toxicity.
CWS-3	Synthesis of Organic Arsenical Compounds.
CWS-4	Methods of Preparation of Certain Non-Arsenical Organic Compounds.
CWS-6	Chemical Detection of Persistent Chemical Agents.
CWS-9	Manufacturing Process for Lewisite.
CWS-13	Catalyst for Prevention of Corrosion of Steel Containers by Liquid Vesicants.
CWS-14	Methods of Analysis and Detection of Chemical Agents in Water and Methods of Purification of such Water.
CWS-21 (Ext. 1)	Investigation of the Physiological Effects from Radiant Heat and High Temperatures on Humans.
CWS-23	The Formation of Flexible Films from Domestic Raw Materials.
CWS-24	The Development of Protective Clothing.
CWS-29	An Investigation of Non-Volatile Toxic Agents and Means for their Use.
CWS-32	Toxic Chemicals for Insect and Rodent Control.
NA-174	Investigation of Gas Generating and High Energy Compounds.
NL-B7	Preparation of Compounds for Study of Thin Films, Especially for Lubrication Problems.
NL-B8	Preparation of Organic Compounds for Gasoline Studies.
NL-B25	Develop a Test Suitable for Shipboard Use for Determining when Impregnated Clothing Has Lost Its Resistance to Mustard Gas.
NL-B27	Develop and Prepare More Stable Compounds for Protective Clothing Giving Protection against Mustard and Lewisite with Particular Consideration to Stability under Conditions of High Temperatures and Humidity Combined with Salt Spray.
NL-B30	Develop and Produce Suitable Compounds for Decontaminating Metal and Painted Surfaces Exposed to Mustard Gas and Lewisite.
NL-B31	Investigation of the Reactions Between Gases such as Mustard and Lewisite and Protective Reagents.
NL-B32	Determination of an Efficient and Simple Indicator for Detecting Mustard Gas in Low Concentrations.
NL-B33	Develop Methods for Quantitative and Continuous Determination of Mustard Gas and Lewisite in Air Either in the Vapor Phase or with the Use of Suitable Absorbers.
NL-B35	The Stability and Hydrolysis of Mustard Gas and Lewisite in Vapor Phase at High Humidities in Presence of Fog and in Presence of Salt Spray.
NL-B41	Preparation of Fluorocarbons and Study of Their Properties as Possible Lubricants.
NO-160	Protection of Personnel Handling Enemy Explosives.
SC-6	Insect Repellents, Insecticides, and Larvicides.
SC-7	Malaria.

INDEX

The subject indexes of all STR volumes are combined in a master index printed in a separate volume. For access to the index volume consult the Army or Navy Agency listed on the reverse of the half-title page.

AC war gas
  see Hydrogen cyanide
Acetylcholine, mustard poisoning role, 446–447
Aconitine, 204
Adamsite preparation, 86
Adenosine triphosphate (AT^P), 191
Aerobic metabolism, inhibition by vesicants, 499
Aeropulse motor gasoline, 630–640
Aerosols
  see Particulate clouds
A/G (albumin-globulin plasma protein ratio), 445
Air, hot, exposure to,
  see Cutaneous exposure to hot air
Airplane fabric damage from gas attacks, 574
Airplane sprays
  lewisite discharge, 93–94
  optimum particle size, 209
Albumin-globulin plasma protein ratio (A/G), 445
Alcohol derivatives, aliphatic, 242-244
Alginic acid salts, 541-542
Aliphatic alcohol derivatives, 242-244
Aliphatic amines, 304–395
Aliphatic fluorine compounds, 156–172
  as food and water poisons, 171–172
  as rodenticides, 172
  as war gases, 156, 170–171
  chemical properties, 162–163
  compared with other agents, 170–171
  physiological mechanism, 167–169
  summary, 157–161
  synthesis, 156–162
  table of compounds, 157–161
  theoretical mechanism of action, 167–169
Aliphatic fluorine compounds, toxicity, 163–170
  animal toxicity, 165–167
  chemical structure, relation to toxicity, 163–165
  human toxicity, 170
  inhalation toxicities, 166
  therapy, 169
Aliphatic nitrosocarbamate (KB-16), 115–130
  as war gas, 115, 130
  chemical properties, 118–119
  compared with mustard gas, 130
  decontamination, 120
  detection, 119–120, 123
  physical properties, 118
  protection, 121
  related compounds studied (table), 116–117
  stability, 120
  synthesis, 115–118
Aliphatic nitrosocarbamate (KB-16), toxicology, 119–130
  chemical structure, relation to toxicity, 119–123
  exposure time, relation to toxicity, 123
  eye-injuring action, 126–128
  inhalation toxicity, 123–124
  parenteral injections, 124
  physiological mechanism, 128–130
  skin toxicity, 124
  vesicant action, 125–126
Alkanolamines, preparation, 66
Alkylaluminum hydrides, 637–638
Alkyl-*bis*(β-hydroxyethyl)amines, 66
Alkyl cyanoamidophosphates
  preparation, 140–141
  structure, 131
Alkyldichlorarsines, 85, 95–96
Alkyl fluorophosphates, 607
  preparation, 141–142
  structure, 131
Alkyl β-chloroethyl sulfides, 412–413
Alkylating action of nitrogen mustards, 66
Allergen, use in ricin toxoids, 193
Aluminum, alkyl, hybrides, 637–638
Aluminum borohydride, 635–636
Aluminum chloride, lewisite catalyst, 83
Amine reactions
  summary, 476–478
  with aliphatic nitrosocarbamate (KB-16), 118–119
  with *bis*(β-chloroethyl) sulfide, 404–405
  with nitrogen mustards, 394
Amines
  see also Amines, ethyl-*bis*(β-chloroethyl) (HN1); Amines, methyl-*bis*(β-chloroethyl) (HN2); Amines, *tris*(β-chloroethyl) (HN3); Nitrogen mustard gas
  aliphatic amines, 304–395
  alkanolamines, 66
  alkyl-*bis*(β-hydroxyethyl) amine, 66
  tris-(β-hydroxyethyl) amines, 66
  ethyl-β-chloroethyl-β-hydroxyethylamine, 458–459
  hexamethylenetetramine, 20, 42, 67, 466–467
  hexanitrodiphenylamine, 385
  isopropyl-*bis*(β-chloroethyl)amine, 69, 476
  isopropyl-*bis*(β-hydroxyethyl) amine, 66
  isopropyl-β-hydroxyethylamine, 66
  methyl-*bis*(β-hydroxyethyl)amine, 66
  methyl-β-chloroethyl-β-hydroxyethylamine hydrochloride, 464–466
  β-phenyl-β-chloroethylamine, 423
  propyl-*bis*(β-chloroethyl)amine, 69
Amines, β-chloroethyl, in heterogeneous systems, 423
Amines, β-chloroethyl, in homogeneous solution, 416–423
  characteristic reactions summarized, 416–417
  cyclization, 417–419
  cyclization reversal, 419–420
  dimerization, 421–422
  electron donors, addition of, 422–423
  formulation of reactions, 417
  hydrolysis, 420–421
  summary of reactions, 416–417
Amines, *bis*(β-chloroethyl)
  see Nitrogen mustard gas
Amines, ethyl-*bis*(β-chloroethyl)(HN1), 457–460
  see also Nitrogen mustard gas
  human intoxication, 460
  neurological injury, 458
  pharmacodynamics, 457–458
  pharmacology of hydrolytic derivatives, 458–459
  prophylaxis and therapy, 458
  systemic pathological action, 459–460
  toxicity, 55, 457
Amines, methyl-*bis*(β-chloroethyl) (HN2), 460–470
  see also Nitrogen mustard gas
  aged solutions, 460–461
  cholinergic action, 460–462
  deaths, delayed, 463
  hexamethylenetetramine (HMT) as preventative, 466–467
  human intoxication, 470
  in aqueous solution, 309–310
  in bicarbonate solution, 310–311
  leucopenia therapy, 467
  leucotoxic action, 469–470
  muscarinic and nicotinic action on blood pressure, 462
  neurological injury, 458
  paralytic action, 462–463
  peripheral circulatory failure, 463

pharmacology of derivatives and transformation products, 464–466
sodium thiosulfate as preventative, 466
systemic injury, 468–469
systemic injury prevention, 466–467
toxicity, 460–461
Amines, *tris*(β-chloroethyl) (HN3), 470–473
see also Nitrogen mustard gas
death, 470–471
determination methods, 604–605
human intoxication, 475–476
ingestion effects, 475
intravenous injection, 473–475
occlusion of blood supply, effect on intoxication, 472
systemic intoxication, prevention, 472
systemic pathologic action, 474–475
toxicity, 55, 470
transformation products, pharmacology, 471–472
transformations in water, 303
vapor toxicity, 154
Anaerobic glycolysis, inhibition by vesicants, 500
Anemia, caused by (β-chloroethyl)sulfide, 446
Antimalarial intermediates and drugs, 651–652
Antimony trichloride, lewisite catalyst, 84
Antiricin, 193–196
animal immunization, 195–196
hemagglutination, inhibition, 193
human immunization, 196
passive immunity, 194
potency, 193
purification, 193–194
therapeutic use, 194
toxicity-neutralization, 193
Apnea induced by phosgene, 18
Aromatic arsenicals, 86
Aromatic carbamates, 204–245
antidotes, 208
chemical structure and toxicity relationship, 208–210
early development, 204
naphthalene derivative carbamates, 240–241
optimum compounds, 204–205
physiological effects, 208
quinoline derivative carbamates, 241–242
stability, 207
synthesis, 205–207
Aromatic carbamates (tables), toxicology, 210–245
benzene compounds with one carbamate group
alkyl side chain having a quaternary ammonium group, 235–239
no quaternary ammonium group, 211
one quaternary ammonium group in the meta position, 216–219
one quaternary ammonium group in the meta position and other substituents, 221–225
one quaternary ammonium group in the ortho position, 214
one quaternary ammonium group in the ortho position and alkyl groups, 214–215
one quaternary ammonium group in the para position (including thiocarbamates), 225–227
one quaternary ammonium group in the para position and other substituents, 227–235
one sulfonium or arsonium group, 240
two quaternary ammonium groups, 239–240
benzene compounds with two carbamate groups and no other groups, 212
benzene compounds with two carbamate groups and other groups, 212–214
benzene compounds with three carbamate groups and no other group, 214
carbamates of aliphatic alcohol derivatives, 242–244
carbamates of naphthalene derivatives, 240–241
carbamates of quinoline and isoquinoline derivatives, 241–242
carbamides and carbazates, 245
miscellaneous carbamates, 244–245
Arsenical antidote
see BAL, arsenical antidote
Arsenicals, 83–114
aliphatic arsenicals, 85–86
alkyldichloarsines, 85, 95–96
aromatic arsenicals, 86
arsine, 97–112
as irritant smokes, 112–114
as warfare agents, 89–112
chloroarsine derivatives, 93–97
detection, 582–583
determination by titration, 605–606
dialkylchloarsines, 85
diphenylaminechloarsine (DM), 112–114
diphenylchloarsine (DA), 112–114
diphenylcyanoarsine (DC), 112–114
heterocyclic arsenicals, 86–87
lewisite, 83–85, 87–93
physical properties, 90–112
table of compounds, 90–112
tertiary arsines, 85
water contamination, 625
Arsine, 97–112
as warfare agent, 98
derivatives, nonhalogenated, 99–112
hemoglobin destruction, 97–98
incapacitating vs. lethal dose, 98
physiological action, 97
therapy, 98
toxicity for dogs, 98
toxicity for man, 98
Arterial blood pressure, animals exposed to excessive heat, 372–375
Aryl β-chloroethyl sulfides, 412–413
ASC charcoal, 11
Atomizers, 286–292
Beneah machine, 287–289
Binks, 290
concentric, 286–290
constant-flow, 289
dry dusting, 291
electrical, 291
impinging, 294
multiple jet, impinging, 290–291
ATP (adenosine triphosphate), 191

B1, ricin product, 186
BAL, arsenical antidote, 570–571
BAL glucoside, 571
chemical analogs, 571
Peters' hypothesis, 433
summary, 94–95
synthesis, 570
therapeutic preparations, 570–571
Bart reaction of grignards, 86
Beneah atomizers, 287–289
Beneah micropipet, 309–301
Benzene compounds (tables), 211–240
one carbamate group, no quaternary ammonium group, 211
one carbamate group and an alkyl side chain having a quaternary ammonium group, 235–239
one carbamate group and one quaternary ammonium group in the meta position, 216–219
one carbamate group and one quaternary ammonium group in the meta position and other substituents, 221–225
one carbamate group and one quaternary ammonium group in the ortho position, 214
one carbamate group and one quaternary ammonium group in the ortho position and alkyl groups, 214–215

one carbamate group and one quaternary ammonium group in the para position (including thiocarbamates), 225-227
one carbamate group and one quaternary ammonium group in the para position and other substituents, 227-235
one carbamate group and one sulfonium or arsonium group, 240
one carbamate group and two quaternary ammonium groups, 239-240
two carbamate groups and no other, 212
two carbamate groups and other groups, 212-214
three carbamate groups and no other group, 214
Benzyl β-chloroethyl sulfide
cutaneous penetration, 490
toxicity, 54
Bernoulli principle in atomizers, 286
Beryllium compounds as hydroquine fuels, 638
Bile reaction to (β-chloroethyl) sulfide, 450
Binks atomizer, 290
Biochemical changes in vesicant-treated skin, 499-502
aerobic metabolism, 499
anaerobic glycolysis, 500
enzyme inactivation, 499
enzyme liberation in skin, 500-502
hexokinase theory of vesication, 500-501
metabolic changes, 499-500
pyrophosphatase activity, 501
pyruvate oxidation inhibition, 501
Blood
changes from mustard gas poisoning, 440-441
changes from ricin poisoning, 190
pooling in hyperemic burns, 347-348
vessels of porcine skin, 327-328
Blood changes after cutaneous hyperthermia, 350-368
first-degree reactions, 341
hemolysis, 363-368
perfusion of heart-lung preparation, 360
plasma turbidity, 359-360
potassium concentration changes, 361-362
pressure changes, 372-375
Blood changes from (β-chloroethyl)sulfide, 444-446
albumin-globulin plasma protein ratio, 445
anemia, 445
coagulation time, 453
electrophoretic pattern, 445
hemoconcentration, 445
leucopenia in men, 453
lipemia, 450
NPN (non-protein nitrogen) rate, 445-446
occlusion of blood supply, 449
plasma concentration changes, 442-444
red cell count changes, 445, 453
Boltzmann-Maxwell energy distribution law, 351
Bombs
chemical reactions after release, 22
lewisite discharging, 93
M47A2 gas bomb, 120
mustard gas, thermal bomb, 57
nitrogen mustard gas bomb, 67
ricin dispersing, 201-202
Bradypnea, result of cutaneous hyperthermia, 375-376
Breuer's work on animal muscle, 315
Bromate-bromide thiosulfate titration of mustard gas, 604
Bromine titration of mustard gas, 602
Bronchiolar injury from phosgene, 20
Bubblers
gas dispersal use, 286
gas sampling use, 596-600
low-resistance absorber, 293
vapor sampling use, 292-293
Burns on skin
see Cutaneous burns
Butyrates
methyl-γ-fluorobutyrate, 161
methyl-γ-fluoro-β-hydroxybutyrate, 162

Cadmium
as warfare agent, 173-175
cadmium oxide smoke, 174-175
cadmium oxide toxicity, 174
delay of toxic effects, 174-175
physiological action, 173-174
toxicity of compounds, 174
Caloric uptake rate
of human skin, 308
of pig skin, 316
Caloric, definition and concept, 307
Carbamates, aromatic
see Aromatic carbamates
Carbamides, 245
Carbazates, 245
Carbon, activated, 536-537
Carbon monoxide
released by iron and nickel carbonyls, 176
role in carbonyl poisoning action, 177-178
Carbon monoxide determination, 620-623
analytic methods, 620
characteristic reactions, 621
colorimetric instruments, 622
detection, 623
exothermic oxidation over Hopcalite, 621-622
hemoglobin reaction analysis, 622
photoelectric instrument, 622
thermometric instruments, 621-622
Carbon-treated fabrics, 538-569
agents against which effective, 561
decontamination, 552, 574-575
disadvantages, 569
droplet penetration into cloth, 561-562
dry-cleaning, 551-552
durability, 558-561, 566-567
laundering, 551-552, 575
summary, 569
Carbon-treated fabrics, deterioration, 549-551
detergent effects, 550-551
mineral oil treatment effects, 550
outdoor exposure effects, 549
perspiration effects, 551
rubber latex fabrics, atmospheric exposure effects, 549-550
S-330 ointment treatment effects, 550
soap treatment effects, 550-551
storage with chloramide-treated cloths, 549
worn garments, 563-564
Carbon-treated fabrics, preparation, 538-548
coating process, 543-545
herringbone twill coated cloth, 543
impregnation by
alginic acid, 541-542
casein ate dispersion, 542-543
methylcellulose system, 539-540
rubber latex binder, 546-541
tetrachlorethane solution of ethylcellulose, 540
rayon fabrics, 545-548
rayon knit fabrics, 546-547
rayon weaving process, 546
rayon yarn, 545
Carbon-treated fabrics, tests, 553-566
gas chamber tests, 557-561
irritancy determined by troop trials, 564-566
laboratory test procedures, 553-561
man-chamber tests, 558-562
Carbonyl chlorofluoride, 23
Carbonyl fluoride, 23
Carbonyls, nickel and iron, 176-178
as warfare agents, 178
carbon monoxide effects, 177
carbon monoxide release, 176
inhalation toxicities, 177

inhalation vs. injection, 178
physiological action, 176–177
role of metal in toxicity, 177–178
summary, 173
Carboxyl groups
reactions with nitrogen mustards, 305
reactions with *bis*-(β-chloroethyl) sulfide, 401–404
Carcinogenesis, inhibition by sulfur mustards, 437
Carcinogenic agents, toxicity, 383
Cardiac changes after heat exposure, 375–376, 380–381
Cascade impactor, 272–274, 295–296
calibration of slides, 274
characteristic mass distribution curve, 273
construction, 272
device for increasing load on slides, 295
dust cloud assessment, 273–274
impingement tendency vs. size measurement, 274
measuring difficulties of aggregates, 273–274
MMD of impacted particles on slides, 272–273
modifications for small particulate sampling, 295–296
nonspherical particle sampling, 273
solid particle sampling, 273–274
summary, 267
Casein, binder for carbon-impregnated fabrics, 542–543
Casein, treated with vesicants, 432
Castor beans
as ricin raw material, 181
ingestion fatal to man, 189
Cattelain process for mustard gas, 30
CC-2 impregnated clothing
see Chloramide-impregnated clothing; Chloramides for vesicant detoxification
CC-2 protective ointment, 527
CECV8 (β-chloroethyl β'-chlorovinyl sulfide), 39
Cellosolve mustard mixtures, 510–511
Cells, damage from mustard gas
see Mustard gas effect on enzymes and cells
Cells, role in thermal injury, 351–354
cell volume increase, 365
energy and entropy of activation, 353–354
fat cell death theory, 352
latent thermal injury, 354
metabolic process alterations, 352
nonprotein-induced alterations in physical characteristics, 352–353
structure and activity of cells, 351
summary, 354
thermal alterations in proteins, 351–352
Cellulose, carbon-treated fabric binder, 537–538
Cerebrospinal fluid, colloidal gold curve, 450
Cerimetric titration of arsenicals, 605
CG war gas
see Phosgene
CH war gas, 406, 454
Chambers for gas studies
see Gassing chambers; Precision gassing
Cheer's systemic hyperthermia studies, 368–369
Chemical warfare agents, summary of all compounds examined, 3–6, 247–264
Chloramide-impregnated clothing, 525–530, 553–569
agents against which effective, 561
aqueous solution impregnation process, 533–534
aqueous suspension impregnation process, 531
droplet penetration into cloth, 561–562
duration of protection, 558
effective life of fabrics, 534–535
exposures per garment, 560
field impregnating sets, 531–533
impregnation systems still uninvestigated, 534
impregnite content determined, 623
rate of loss of impregnite, 567–569
reimpregnated garments, 563–564
research recommendations, 534–535
spray protection, 561
stabilization of impregnated fabrics, 530
storage with carbon-treated fabrics, 549
summary, 569
tetrachloroethane solvent, 529
worn garments, 563–564
Chloramide-impregnated clothing, tests, 553–566
field tests, 562
gas chamber tests, procedure, 557–558
irritancy determined by troop trials, 564–566
laboratory test procedures, 553–556
man-chamber tests, 558–562
Chloramides for vesicant detoxification, 521–524, 572–574
CC-2 impregnite, 521–522
Decontaminant 40, 524
dispersion systems, 573–574
formulations, 573
Impregnite E, 521–522
nitrogen mustard detoxificant, 524
ointments, 525–528
reactions with vesicants, 572
requirements, 521
S-210 impregnite, 523
S-328 impregnite, 522
S-330 impregnite, 521, 523–524
S-436 impregnite, 524
S-461 impregnite, 522–523
solution systems, 573
Chloramine-T titrations of mustard gas, 602
Chlorarsines, 95–97
see also Lewisite
alkyldichlorarsines vapor toxicity, 95–96
dichlorarsines vapor toxicity, 96
eye effects, 96–97
German development, 95
military value, 97
percutaneous toxicity, 96
physiological action, 95
vesicant properties, 96
Chloride ion potentiometric determination, 618
Chloroacetophenone (CN) determination, 607
β-Chloroethyl compounds
see Amines; Ethane; Ether; Ethylenimonium; Sulfides
β-Chloroethyl groups of Q reactions with compounds of biochemical interest, 414
β-Chloroethylsulfenyl chloride in mustard gas formation, 40
β-Chlorovinyldichlorarsine
see Lewisite
Cholinergic action
of methyl-*bis*(β-chloroethyl)-amine, 461–462
of mustards, 441
Chromosomal mechanism affected by vesicants, 437
Circulatory failure from heat exposure, 368–381
arterial blood pressure, 372–373
bradypnea, 375–376
cardiac changes due to potassium ion, 380–381
cardiovascular failure vs. respiratory insufficiency, 378–380
early investigation summarized, 368–370
electrocardiographic changes, 376–378
immersion temperatures, 378–380
plasma potassium changes, 378
respiratory rate fluctuations, 375–376
summary, 381

CK war gas
see Cyanogen chloride
Clothing, protective, 529-569
carbon-treated fabrics, 538-569
chloramide-impregnated clothing, 529-535, 553-569
insect repellent impregnated cloth, 640
vesicant burn protection, 514
Clouds
see Particulate clouds
CN (chloroacetophenone), 607
Coagulation necrosis, vesicant induced, 482
Coagulation of particles, 269
Colloidal gold curve of cerebrospinal fluid, 450
"Competition factors"
bis-(β chloroethyl)sulfide, 400-401
sulfur mustards in homogeneous solution, 127-428
Compounds examined as warfare agents, summary, 3-6, 247-264
Concentration sampling equipment
see Sampling equipment for toxicological studies
Conduction, heat transfer role, 308
Convection, heat transfer role, 308
Convulsive action of mustards, 442
Corn oil, nasal filtration use, 298
Corneal epithelium loosening, 436
Crayons for detection of warfare agents, 586
Crozier's work on life processes, 353
Cryoscopic analysis of DDT, 643
Cuprous chloride, lewisite catalyst, 83
Cuprous iodide test for arsenicals, 582
Cutaneous burns, 329-350
cumulative effects of repeated subthreshold exposures, 337
epidermal destruction, 334-336
experimental procedure for surface temperature control, 329-330
human skin time-temperature thresholds, 332-333
inverse relationship, time and temperature, 330-332
ischemic skin vulnerability, 336-337
latent injury after repeated exposures, 337
mathematical predictability of epidermal destruction, 334-336
necrosis, recognition criteria, 330
pig experiments, 330
subthreshold vs. threshold exposure, 330-332
summary, 337-338
vulnerability, human vs. porcine skin, 333-334
Cutaneous burns from heat, 338-350
see also Cutaneous tissue changes after burns; Heat transfer to skin
compared with vesicant burns, 484
degree of reaction defined, 339
depth and quality of burn, relationship, 339-340
experimental procedures, 338-339
qualitative differences in similar reactions, 340
Cutaneous burns from heat, first-degree reactions, 341-344
circulatory failure, 341
cyanosis, 341
edema, 341
epidermal anchorage, reversible impairment, 342
epidermal cells, irreversible thermal injury, 342-344
nuclear changes in epidermal cells, 342-344
vascular reactions, 341
Cutaneous burns from heat, second-degree reactions, 344-346
transepidermal necrosis, 344-345
vesication, 345-346
Cutaneous burns from heat, third-degree reactions, 346-350
compressive hyperthermia, effect on burn color, 348-349
epidermal changes, 346
hyperemic burns pooling of blood, 347-348
miscellaneous effects of heat on dermis, 349-350
red and pale burns, 346-347
Cutaneous burns from vesicants, 479-519
see also Cutaneous penetration by vesicants
biochemical changes, 499-502
capillary permeability, 484-486
circulatory changes, 484-486
coagulation necrosis, 482
compared with thermal burns, 484
epithelial cell, transplanting, 486
healing time, 481
histamine-like substance release, 485
histological studies, 481-482
human vs. animal skin response, 482-483
incapacitation degree prediction, 480-481
intercellular substances affected by vesicants, 486
leucotaxine-like substance release, 485-486
molecular structure and vesicancy, 505-507
morphological evidences of injury, 484
progressive severity, types of injuries, 479-480
skin-grafting experiments, 486
subvesicating injuries, histological category, 48
summary, 479, 486-487
time course in development of injury, 480-481
vesication of animal skin, 483-484
Cutaneous burns from vesicants, prevention, 513-518
decontamination, 515-516
definitions, 513-514
protective clothing, 514
protective intradermal administration, 514-515
treatment of early stages, 516-517
treatment of late stages, 517
Cutaneous exposure to gasoline conflagrations, 305-306
Cutaneous exposure to hot air, 354-362
animal experiments summarized, 356-358
blood changes, 359-362
calorie uptake of pig skin, 356
comparison, hot air vs. hot water effects, 357
death, 359
experimental procedure, 354-356
heat transfer measurements, 355-356
human sweating, protection against injury, 358-359
pathological changes, 359, 361-362
perfusion experiments, 360
plasma turbidity, 359-360
potassium content of blood, 361-362
summary, 362
temperature and survival, relationship, 360
temperature-time relationship, necrosis production, 357-358
Cutaneous penetration by vesicants, 487-498
entry channels into skin, 488
evaporation of vesicant from skin, 487-488
exposure time and amount of penetration, 490
"fixation" of vesicant in skin, 487
fixed vesicants, chemical properties, 498
fixed vesicants, correlation with severity of injury, 495-497
fixed vesicants, disappearance rate, 497
fixed vesicants, distribution within skin, 497-498
ice-pack treatments, 493-494
local fate of vesicant, 10 minute exposure, 492-493
local fate of vesicant, 1 hour exposure, 492
penetration rates, 488-491

saturated vapor penetration, 490–491
saturated vapor vs. liquid penetration, 491
summary, 494
temperature effect on penetration rate, 491
Cutaneous sensitization to vesicants, 502–505
degree of hypersensitivity, 504
desensitization, 505
guinea pig sensitization, 503–505
human sensitization, 502–503
induction of hypersensitivity, 503–504
onset time of hypersensitivity, 504
prevention, 504
sensitivity to vapor, 503
serum protein complexes, 505
susceptibility, normal vs. sensitized animals, 504
Cutaneous tissue changes after burns, 350–354
activation energy, experimental equations, 353–354
entropy of activation, experimental equations, 353–354
kinetics, physical and chemical processes, 351
latent injuries, 354
living cell attributes, 351
metabolic reactions, thermal injury role, 352
nonprotein-induced alteration in cells, 352–353
summary, 354
thermal alterations in proteins, 351–352
CWS "dynamic test" for protective clothing, 554
Cyanide poisoning
see Cyanogen chloride; Hydrogen cyanide
Cyanogen chloride, 7–16
as a war gas, 16
as water contaminant, 625
detectability limit, 11
detection methods, 583
detoxification rate by man, 11
lethal dose, 12
pathological effects, 15
physical properties, 7, 29
physiological effects, 15–16
polymerization causes, 8
respiratory stimulation, 12, 13
skin irritancy, 15
susceptibility of animal species, 13–14
tests with sodium pyrophosphate stabilizer, 9
toxicity, 11–15
toxicity relative to phosgene, 19–20
Cyanogen chloride, stability
instability due to water and steel, 9, 10
particle size and stability, 10
purity specifications for stability, 10
stability in storage, 8–10
Cyanosis, 341
Cyon's systemic hyperthermia study, 389
Cytolytic action of mustards, 440–441

DA (diphenylchlorarsine), 112–114
DANC decontaminating system, 573
DAP (diamisylpropylene) arsenical detection test, 582
DH-3 test
for mustard gas, 53, 581, 603
for nitrogen mustards, 68, 604–605
DC (diphenylcyanoarsine), 112–114
DDT, 641–646
composition, 641–642
odor control concentrates, 646
pastes, dispersible, 645
powders, dispersible, 644–645
resistance to caking, 641
solvents, 645
spreading agents, 646
surface-active agents for emulsion concentrates, 645
DDT determination, 642–644
color test, 643–644
cryoscopic analysis, 643
lacquered surface detection, 643
phosgene estimation method, 643
spectroscopy, infrared, 642–643
spectroscopy, ultraviolet, 643
Decontaminated-40, vesicant detoxificant, 524
Decontamination, 572–576
airplane fabrics, damage from decontamination, 574
bleach slurry thickening, 575
chloramide dispersion systems, 573–574
chloramide reactions, 572
chloramide solutions, 573
definition, 572
emulsion paste system, 574
factory damage from decontamination, 574
formulations, 573
of carbon-treated fabrics, 552, 574–575
of nitrogen mustards, 68
testing, 575–576
Decontamination of vesicant burns, 515–516
chemical vs. mechanical decontamination, 516
temperature effect, 515
time factor, 515
vapor burn decontamination, 516
Degree of hazard from warfare agents, 579–580
Density of lethal vapors, tactical importance, 7
Dermatitis caused by hexanitrodiphenylamine, 385
Dermis, porcine vs. human, 326–329
blood vessels, 327–328
sweat glands, 328–329
Detection of warfare agents, 581–587
see also Identification of warfare agents
arsenicals, 582–583
by crayons, 586
by detector kits, 586–587
by paints, 585–586
by powders, 586
carbon monoxide, 623
disulfur decafluoride, 25
fluorines, 583
identification vs. detection, 581
mustard gas, 581–583
vapors, 584–585
Detector kits, 586–587
British vapor kit, 586
enemy detector kits, 587
M-9 vapor kit, 586
Navy Mark I vapor kit, 587
OCD kit, 587
paper kit, 587
security division kit, 587
vesicant gas kit, 587
water test kit, 587
Detergents, synthetic, 550–551
Determination of warfare agents, 602–619
arsenical determination, 605–606
carbon monoxide determination, 620–623
fluorine compound determination, 606–607
mustard gas determination, 602–605
tape recorders, 614–618
titrimeters, 609–614
Dialkylchlorarsines, 85
Dialkyl fluorophosphates, 132–150
analysis and detection, 143
chemical reactions, 142–143
compared with Trilons, 132
decontamination, 144
detection, 583
eye effects, 145–150
preparation, 132–139
properties, 132
protection, 141
stability, 143–144
structure, 131
Dialkyl hydrogen phosphite synthesis of diisopropyl fluorophosphate (DF-3), 138–139

Diamidophosphoryl fluorides
preparation, 139–140
structure, 131
toxicity, 132
Diamyl disulfide, 43
Dianisylpropylene reagent for arsenical detection, 582
Dichlorarsine, β-chlorovinyl
see Lewisite
Dichloro-diethylsulfide
see Mustard gas
Dichloroformoxime, 246
Dicyclohexyl fluorophosphate
preparation, 138
structure, 131
toxicity, 153
Diethyl fluorophosphate
eye effects, 147
structure, 131
toxicity, 152
Diisopropyl fluorophosphate (PF-3), 142–152
chemical reactions, 142–143
decontamination, 144
detectability by odor, 144–145
dialkyl hydrogen phosphate synthesis, 138–139
eye effects, 147–150
preparation, 138–139
protection, 144
stability, 143–144
structure, 131
toxicity, 152
1,2-dimercaptopropanol
see BAL, arsenical antidote
Dimethyl fluorophosphate (PF-1)
chemical reactions, 142–143
decontamination, 144
detectability by odor, 144–145
eye effects, 147
phosphoryl chloride preparation method, 138
pilot plant preparation, 139
protection, 144
stability, 143–144
structure, 131
toxicity, 152
vapor toxicity, 154
Diphenylaminechlorarsine (DM), 112–114
Diphenylchlorarsine (DA), 112–114
Diphenylcyanarsine (DC), 112–114
Diphenyl disulfide, 43
Diplosgene, 21–23
conversion to phosgene in shell, 21–22
dissociation phenomena, 22
physical properties, 21
pilot-plant production, 21
preparation, 21–22
toxicity, 23
Di-sec-butyl fluorophosphate
eye effects, 150
structure, 131
toxicity, 153
Disulfides
diamyl disulfide, 43
diphenyl disulfide, 43
Disulfonium dichloride, 8,8'-endoethylene-1,4-dithiane, 407
Disulfur decafluoride, 24–29
as a war gas, 29
canister penetration, 25
chemical properties, 24
detection, 25, 583
exposure symptoms, 26
odor, 26
pathologic effects, 27
physical properties, 24, 29
physiological effect, 28
preparation, 24
protective measure, 28
stability, 25
toxicity for various species, 26
Dithiane in mustard gas, 39
β-chloroethyl-1,4-Dithiane sulfonium chloride, 407
α-Dithiols detoxification of lewisite, 84
Divinyl sulfide, 456
Divinyl sulfone, 408–412
aqueous solution reactions, 409
nitrogenous base reactions, 409–412
pharmacology, 456
sulfhydryl group reactions, 409
summary, 412
Divinyl sulfoxide reactions, 408–412
aqueous solutions reactions, 409
pyridine reaction, 412
sulfhydryl group reactions, 409
summary, 412
Division 9, NDRC, summary of work, 3–6
DM (diphenylaminechlorarsine), 112–114
DP war gas
see Diplosgene
Drads, vesicant testing micropipet, 299–300
Dry-cleaning of carbon-treated fabrics, 551–552
DTH, antiarsenical agent, 94–95
Dust dispersing atomizer, 291
Dusts, toxic, 173–176
assessment methods, 273–274
cadmium, 173–175
selenium, 383–384
selenium, 175

E-10 chemical agent analyzer, 592
ED (ethyldichlorarsine), 95–97
Eddy currents, heat transfer role, 307
Edema
fluid and skin caloric uptake, 317–318
from cutaneous hyperthermia, 341
of lungs from disulfur decafluoride, 28
Edgewood vapor cups, 301
Edgewood vesicant testing rods, 298
EDS (effective drop size), 272
Electrocardiographic changes after heat exposure, 376–378
Electrolyte metabolism, affected by (β-chloroethyl) sulfide, 447–448
Electrode interval timer for the Northrup titrimeter, 293–294
Electrophoretic pattern of plasma, 445
8,8'-Endoethylene-1,4-dithiane disulfonium dichloride, 407
Enzyme activity of ricin, 191, 200
Enzyme inactivation by vesicants
see Mustard gas effect on enzymes and cells
Enzyme liberation in skin by vesicants, 500–502
Epidermal destruction from heat
see Cutaneous burns
Epidermal temperature of animals
see Heat transfer to skin
Epidermis, pig *vs.* human, 325–326
Equations
caloric uptake rate of skin, 308
cutaneous thermal injury, activation energy, 353–354
epidermal destruction by exposure to heat, 334–336
flow of heat through skin, 309–310
gassing chamber equilibration times, 278
heat conduction, steady state, 308–309
Maxwell-Boltzmann energy distribution law, 351
ricin dose-survival time curves for mice, 188, 199–200
Erythema produced by vesicants, 180
Erythrocytes, 365–368
potassium content, 365–366
swelling with hyperthermia, 366–368
Ethane, 1,2-*bis*(β-chloroethylthio) (Q)
impurity in mustard gas, 39
pharmacology, 156–157
physical properties, 44
preparation, 31
toxicity in drinking water, 57
toxicity to various species, 55
transformations in water, 113–114
vesicancy, 53–54
Ethane, 1,2-*bis*(β-chloroethylthio) (Q), photosynthesis
inhibitors, 44
promoters, 43
reaction mechanism, 43
wavelengths effective, 43–44

Ethane, *bis*(β-chloroethylthio), water contamination, 624
Ethanedithiol, 43, 44
Ethanolamines in nitrogen mustard preparation, 59–66
Ether, *bis*(β-chloroethylthioethyl)
  eye injuring action, 56
  physical properties, 44
  preparation, 31
  toxicity to mice, 55
  transformations in water, 414
  vesicancy, 54
  water contamination, 624
Ethyl-*bis*(β-chloroethyl)amine (HN1)
  see Amines, ethyl-*bis*(β-chloroethyl) (HN1)
Ethylcellulose solution used in carbon impregnation of fabrics, 540
Ethyldichlorarsine (ED), 95–97
N-Ethyl diethanolamine hydrochloride, 65
Ethyl dimethylamidocyanophosphate (MCE), 140–151
  analysis, 143
  chemical reactions, 143
  decontamination, 144
  detectability by odor, 144–145
  determination, 607
  eye injuring action, 146–147
  preparation, 140–141
  stability, 144
  structure, 131
  toxicity, 150–151
  vapor toxicity, 154
Ethyl-β-chloroethyl-β-hydroxyethylamine, 458–459
Ethyl-β-chloroethyl sulfide
  cutaneous penetration, 490
  vesicancy, 54
Ethylene chlorohydrin for thiodiglycol production, 30
Ethylene in mustard gas production, 30
Ethylene oxide for thiodiglycol production, 30
Ethylenesulfonium ion, 424–428
  "competition factors", 427–428
  formation, 424–425
  hydrolysis, 427–428
  kinetics of formation, 425–427
  reactions, 427–428
Ethyleniminonium compounds, 391
  1,1-*bis*(β-chloroethyl) ethyleniminonium chloride, 471
  1,1-*bis*(β-hydroxyethyl)ethyleniminonium chloride, 472
  1-ethyl-1-(β-hydroxyethyl) ethyleniminonium chloride, 459
  methyl-(β-chloroethyl) ethyleniminonium chloride, 464
  1-(β-chloroethyl)-1-(β-hydroxyethyl) ethyleniminonium chlorine, 472
  1-methyl-1-(β-chloroethyl) ethyleniminonium pierylsulfonate, 464
  1-methyl-1-(β-hydroxyethyl) ethyleniminonium pierylsulfonate, 466
Ethyleniminonium ion, 1-(β-chloroethyl), 66
Evaluation of chemical warfare compounds, 3–6, 247–264
Evaporation heat of nonpersistent war gases, 29
Evaporation of vesicants from skin, 487–488
Explosion testing chamber, 284
Eye injuries from
  aliphatic nitrosocarbamate (KB-16) 126–128
  chloarsines, 96–97
  bis(β-chloroethylthioethyl)-ether, 56
  ethyl dimethylamidocyanophosphate, 147
  fluorophosphates, 145–150
  lewisite, 88–92
  mustard gas 56, 78–79
  nitrogen mustard gas, 75–78
  phosphorus compounds, 145–150
  bis(dimethylamido) phosphoryl fluoride, 150
  ricin, 188–189
Eye therapy with BAL, 570

Fabrics, carbon-treated
  see Carbon-treated fabrics
Factory damage from gas attack and decontamination, 574
Fat cells, liquefaction in thermal injury, 352
Ferris' systemic hyperthermia studies, 369
Fick's systemic hyperthermia studies, 369
Field sampling procedures, 594–601
  area distribution, 595
  area vs. line sampling, 594
  bubblers, 599–600
  continuous vs. intermittent sampling, 595
  flow rate, low vs. high, 597
  installations, developed vs. temporary, 597
  liquid contamination determination, 600
  prolonged sampling, 596
  pump units, 597–599
  topographical factors, 595
  with nitrogen mustard gas, 79–80
Flame thrower attacks, casualty production
  see Heat exposure casualties
Flash inhibitors for hydrogen cyanide munitions, 8
Fluoride ion detection, 25, 583
Fluorine atom removal from molecule, 162
Fluorine compounds
  aliphatic; *see* Aliphatic fluorine compounds
  as water contaminants, 625
  detection, 583
Fluorine compounds, determination methods
  ammonia decomposition, 606
  periodate-perchlorate decomposition, 606–607
  pyrolytic decomposition, 606
  sodium decomposition, 606
  sodium peroxide decomposition, 606
Fluoroacetate
  see Methyl fluoroacetate
Fluoroacetic acid and derivatives
  see Aliphatic fluorine compounds
Fluorocarbons, 629–633
  carbon and fluorine reaction, 629–630
  halogen replacement by fluorine, 631
  high molecular weight fluorocarbons, 632
  hydrogen replacement by fluorine, 630–631
  nitro or amino group replacement, 631
  polymerization of small units, 632
β-Fluoroethanol, 161
Fluorophosphate compounds
  see also Diisopropyl fluorophosphate (PF-3); Dimethyl fluorophosphate (PF-1)
  alkyl fluorophosphate, 131, 141–142, 607
  dicyclohexyl fluorophosphate, 131, 138, 153
  dialkyl fluorophosphate, 132–150
  diethyl fluorophosphate, 131, 147, 152
  di-sec-butyl fluorophosphate, 131, 150, 153
  isopropyl ethanefluorophosphonate, 131, 151
  isopropyl methanefluorophosphonate (MF-1), 131, 141–142, 151, 154
  table of compounds, 133–137
Fluorophosphates, 131–155
  analysis and detection, 143
  chemical reactions, 142–143
  decontamination, 144
  detectability by odor, 144–145
  eye effects, 145–150
  pathology, 153–154
  physiological mechanism, 155
  preparation, 132–139
  properties, 132

protection, 144, 154 155
skin effects, 154
stability, 143
structure, 131-132
summary, 133-137
toxicity, 150-154
Food poisoning from methyl fluoroacetate, 171
470 BM 199, ricin product, 196
Fourier equation, flow of heat through skin, 309
Fractionating devices, 291–292
fractionating tower, 291
rotating macro-impinger, 291
serial macro-impinger, 291
summary, 295
French (Cattelain) mustard gas process, 30
Fuels, hydropulse, 634-640
alkylaluminum hydrides, 637-638
aluminum borohydride, 635-636
beryllium compounds, 638
lithium borohydride, 636 637
lithium hydride, 635
test methods, 638–639
Fulminic acid salts, 246
Furan arsenicals, 86

Gas dispersal into chambers, 285–292
atomizers, concentric, 286–290
atomizers, electrical, 291
atomizers, impinging, 290–291
bubblers, 286
dispersal techniques, 285–286
fractionating devices, 291 292
summary, 285
Gases, war
see War gases
Gasoline adjuvants for aeropulse motors, 639 640
Gasoline conflagrations, 303–307
animal exposure, cutaneous and respiratory, 304 306
burning experiments, 303
cutaneous exposure, 306
flame thrower attacks, probable temperature, 304
respiratory exposure, 306
summary, 306–307
temperatures, 304
Gasoline fumes, toxicity, 383
Gassing chambers, 278-285
200-liter medium flow, 280 281
400-liter standard chamber, 280
420-liter glass-lined chamber, 281
880-liter chamber, 280
explosion chamber, 284
Great Lakes man-chamber, 282-283
incinerator chamber, 282
microdine, 283
screening smoke chamber, 281 282
smoke chamber, 283
wind tunnel, 284-285
Gassing chambers, design factors, 278–280
air flow measuring equipment, 279
chamber equilibration time, 278
dispersal of gas from chamber, 285–286
filtration of effluent, 279
flow of air through chamber, 278
introduction of animals into chamber, 279–280
temperature and humidity control, 280
variables affecting chamber conditions, 278
Gassing chambers, dispersal into, 285–292
concentric atomizers, 286-290
design problem, 279–280
electrical atomizers, 291
fractionating devices, 291-292
impinging atomizers, 290–291
Gastric secretions effected by (β-chloroethyl) sulfide, 447
Glycolysis, anaerobic, 560
Gold chloride-benzidine colorimetric determination of mustard gas, 604
Grant and Lewis' theory of histamine release in cutaneous injury, 485–486
Great Lakes man-chamber, 282–283
Ground contamination by lewisite, 93
Guthrie process for mustard gas, 30

H war gas
see Mustard gas
Half life of aerosol, 269
Halogen fluorine replacement, 631
HB process for mustard gas, 32
HBD process for mustard gas, 32
HCD process for mustard gas, 32
"Heat capacity", 307
Heat exposure casualties, 303–381
circulatory failure and death, 368–381
cutaneous burns, 338-350
cutaneous exposure to hot air and radiant heat, 354-362
gasoline conflagrations, 303-307
heat transfer and thermal injury, 307-320
hyperpotassemia, 362-368
physical and chemical changes in tissue, 350-354
respiratory damage, 320-325
skin, human vs. porcine, 325-329
Heat transfer to skin, 307-320
caloric uptake of skin, 316
caloric uptake rate of skin, 308
conduction, 308 309
convection, 308
dermal-fat interface temperature, time dependence, 317–318
epidermal temperature when skin is immediately brought to specific heat, 318-319
epidermal temperature when skin is surrounded by heat, 319–320
flow of heat through skin, 309–310
heat capacity, 307-308, 315
"in vivo" factor, skin temperature as time function, 309
nature of heat, 307
radiation, 308
steady-state vs. unsteady state conduction, 308-309
summary, 320
thermal conductivity of animal tissues, 315
thermal conductivity of pig tissues, 315–316
Heat transfer to skin, assessing apparatus, 310–315
energy recording applicator, automatic, 311–313
heat capacity apparatus, 310
thermocouple for measuring surface-skin temperatures, 314–315
thermocouple for measuring temperatures beneath exposure, 313–314
Hemagglutination test for ricin, 197, 200
Hemoglobin destruction by arsine, 97-98
Hemoglobin reaction with carbon monoxide, 622
Hemolysis from cutaneous hyperthermia, 363–368
accompanies fatal plasma levels, 368
exposure at 47C, no hemolysis, 363
exposure to 75C, 363–366
in vitro effects of heat, 366–365
Herringbone twill cloth, carbon coating, 543
Heterocyclic arsenicals, 86–87
Hexamethylenetetramine
as methyl-*bis*(β-chloroethyl)-amine preventative, 466–467
as mustard gas stabilizer, 42, 67
as prophylactic against ketene, 20
Hexanitrodiphenylamine, dermatitic agent, 385
Hexokinase theory of vesication, 500-501
Heymans' systemic hyperthermia studies, 368-369
Histamine-like substances released in cutaneous injuries, 485-486
Histidine, imidazole group, 494-495

HM process for mustard gas, 32
HMD process for mustard gas, 32
HMT (hexamethylenetetramine), 466–467
HN1 war gas
  see Amines, ethyl-*bis*(β-chloroethyl) (HN1); Nitrogen mustard gas
HN2 war gas
  see Amines, methyl-*bis*(β-chloroethyl) (HN2); Nitrogen mustard gas
HN3 war gas
  see Amines, *tris*(β-chloroethyl)(HN3); Nitrogen mustard gas
HQ mustard gas mixture
  evaluation for war use, 57
  freezing point, 44–53
  thiodiglycol production process, 31
  toxicity to mice, 55
HS process for mustard gas, 32
HT mustard gas mixture
  evaluation for war use, 57
  freezing point, 44–52
  thiodiglycol production process, 31
  toxicity to mice, 55
Hydraulic fluids
  fluorinated oxygen compounds, 633
  fluorocarbons, 629–633
  thin film studies, 629–633
Hydrochloride, N-ethyl diethanolamine, 66
Hydrogen cyanide, 7–16
  as a war gas, 16
  detection methods, 11, 583–584
  determination, 607
  detoxification rate by man, 11
  flashing in munitions, 8
  lethal dose, 12
  odor detectability, 11
  pathological effects, 15
  physical properties, 7, 29
  physiological effects, 15–16
  respiratory stimulation, 12
  stability in storage, 8
  toxicity, 11–15, 19
Hydrogen peroxide preparation, 640
Hydrogen phosphite (dialkyl) synthesis of diisopropyl fluorophosphate, 138–139
Hydrogen replacement by fluorine, 630–631
Hydropulse fuels, 634–640
  alkylaluminum hydrides, 637–638
  aluminum borohydride, 635–636
  beryllium compounds, 638
  lithium borohydride, 636–637
  lithium hydride, 635
  test methods, 638–639
β-Hydroxyethylamines
  see Amines
Hyperpotassemia from cutaneous hyperthermia
  see Plasma potassium after cutaneous hyperthermia
Hypochlorite titration of mustard gas, 602

Ice-pack treatments on vesicant exposed skin, 493–494
Identification of warfare agents, 588–593
  see also Detection of warfare agents
  analysis procedures, 589–590
  British war gas kit, 592
  derivatives determined, 590
  detection vs. identification, 581
  E-10 chemical agent analyzer, 592
  equipment, 588
  functional group analysis, 590
  microscopic procedures, 591
  mobile laboratories, 591–592
  sample purification, 588–589
  smoke identification kit, 593
  tabular summaries, 590
Imidazole group of histidine, 404–405
Immunological studies
  see Ricin immunology; Vesicant immunology
Impinging devices for particulate sampling, 294–295
Impregnite F, British vesicant detoxificant, 521–522
Indolyl groups of proteins, reaction with vesicants, 432
Infrared spectroscopy for DDT determination, 642–643
Inhalation of heat, 320–325
  alveolar ducts and alveoli injury, 323
  amount of heat in one breath, 323
  amount of heat transfer, skin vs. respiratory tract, 323–325
  cooling rate of inhaled air, 320–322
  experimental procedure, 320
  mucosal necrosis, 323
  primary thermal injury to lungs, 323
  summary, 325
  water content of inhaled gas, 324
Inhalation toxicities
  see Respiratory damage
Inhaled volume per breath, 12
Insect control, 641–650
  DDT composition, 641–642
  DDT determination, 642–644
  DDT formulations, 644–646
  miticides, 650
  repellent impregnated cloth, 649
  repellent protection time, 648–649
  repellent skin tests, 646
  "6-2-2" repellent, 646
Intestinal secretions, effect of exposure to (β-chloroethyl) sulfide, 447
Iodate thiosulfate titration of mustard gas, 604
Iodometric titration of arsenicals, 605
Iodoplatinate test for mustard gas, 582, 603
Iron carbonyl, 176–178
  as warfare agent, 178
  carbon monoxide release, 176
  inhalation vs. injection, 178
  parenteral administration, 177–178
  physiological action, 176–177
  summary, 173
  toxicity by inhalation, 177
Iron containers, effect on mustard gas, 30
Ischemia, effect on skin vulnerability to thermal injury, 336–337
Isopropyl-*bis*(β-chloroethyl)amine
  see also Nitrogen mustard gas
  pathology, 476
  toxicity, 69, 476
Isopropyl-*bis*(β-hydroxyethyl)amine, 66
Isopropyl ethanefluorophosphonate
  structure, 131
  toxicity, 151
Isopropyl-β-hydroxyethylamine, 66
Isopropyl methanefluorophosphonate (MF1)
  preparation, 141–142
  properties, 142
  structure, 131
  toxicity, 151
  vapor toxicity, 154
Isoquinoline derivated carbinamines, 241–242

Japanese canisters, penetration by cyanogen chloride, 11
Jet motor fuels
  see Hydropulse fuels

Kabat and Levine's citrated plasma experiments, 359
Kahn's systemic hyperthermia study, 369
KB-16 toxic agent
  see Aliphatic nitrosocarbamate (KB-16)
Ketene, toxic action of, 20
Khurasch lead alkyl process, 85
Knowlton and Starling's hyperthermia studies, 369

L war gas
  see Lewisite
L703, ricin product, 186
Lacquered surface test for DDT, 643
Lacrimator chamber, 282
Lacrimator decontamination, 572
Latex carbon-treated fabrics, 549–550

Lehmann's toxic vapor studies, 278
Lesions from vesicant burns, 480–481
Leucopenia
  methyl-*bis*(β-chloroethyl)-amine induced, 467, 469–470
  (β-chloroethyl) sulfide induced, 453
  therapeutic procedures, 449
Leucotoxine-like substance released by cutaneous burns, 485–486
Levine and Kabat's citrated plasma experiments, 350
Levinstein mustard gas
  see Mustard gas of Levinstein type
Lewis and Grant's theory of histamine release in cutaneous injury, 485–486
Lewisite, 83–85, 87–95
  airplane spray release, 93–94
  blister fluid, 92
  bomb explosion release, 93
  chemical properties, 89
  compared with mustard gas, 88–89, 93–94
  corrosive effect on shell steel, 84
  detoxification agents, 84–85
  ground contamination, 93
  military value, 88
  mustard and lewisite mixtures, 84
  1919 studies, 87–88
  protection, wet vs. dry clothing, 87–88
  protection against liquid, 94
  protection against vapor, 94
  summary, 95
  therapeutic agent, BAL, 94–95
  vapor concentration in field, 93
Lewisite preparation, 83–84
  aluminum chloride as catalyst, 83
  arsenic trichloride preparation, 84
  cuprous chloride as catalyst, 83
  mercuric oxide as catalyst, 83
Lewisite toxicity, 89–94
  compared with mustard gas, 92
  evaluation criterion, 90–91
  eye casualties, 88–89, 91–92
  liquid toxicity, 91
  mechanism of injury production, 487
  parenteral administration, 91
  respiratory tract effects, 88, 90
  skin vesication, 87, 90, 92
  summary, 55, 92–93
  systemic effects, 90–91
  vapor toxicity, 90
Lipemia from exposure to (β-chloroethyl) sulfide, 450
"Lipid pneumonia", 382
Lipoids, liquefaction in thermal injury, 352
Lithium borohydride, 636–637
Lithium hydride, 635
Lubricants, 629–633
  fluorinated oxygen compounds, 633
  fluorocarbons, 629–633
  thin film studies, 629–631
Lung damage
  see Respiratory damage

M-1 chloramide impregnating set, 531
M-1 eye solution, 570
M-3 mobile laboratory, 592
M-4 protective ointment, 525
M-5 protective ointment, 527–528
M-9 vapor detector kit, 580
M47A2 gas bomb, 120
Macro-impinger, 291
Magnesium carbonate disulfur decafluoride protection, 28
Mammalian cells, mitotic inhibition by vesicants, 437–438
Man-chamber tests
  of mustard gases, 74–76
  of nitrogen mustard vapors, 75
  procedure, 282–283
Marine eggs, mitotic inhibition by vesicants, 438
Markownikoff's rule in mustard gas formation, 42
Maxwell-Boltzmann energy distribution law, 351
MC'E war agent
  see Ethyl dimethylamidocyanophosphate (MC'E)
MD (methyldichlorarsine), 95–97
Menkin's studies of inflammatory exudates, 485
Mercaptans, examination for war use, 45
β-Mercaptoethanol, 31
Mercuric oxide, lewisite catalyst, 83
Mercurimetric titration of mustard gas, 603
Metabolic changes in skin
  after heat exposure, 352
  after vesicant exposure, 499–500
Metals, toxic, 173–178
  cadmium, 173–175
  nickel and iron carbonyl, 176–178
  selenium 175
Methemoglobin, use with cyanide poisoning, 15–16
Methyl-*bis*(β-hydroxyethyl)amine, 66
Methyl-*bis*(β-chloroethyl)amine (HN2)
  see Amines, methyl-*bis*(β-chloroethyl) (HN2)
Methylcarbamates
  see Aromatic carbamates
Methylcellulose system of carbon impregnation, 539–540
Methyl chloroformate, 115–117
Methyldichlorarsine (MD), 95–97
Methyl-(β-chloroethyl)ethyleniminonium chloride, 464
1-Methyl-1-(β-chloroethyl)ethyleniminonium picrylsulfonate, 464
1-Methyl-1-(β-hydroxyethyl)ethyleniminonium picrylsulfonate, 466
Methyl fluoroacetate, 150–172
  as war gas, 170–171
  chemical properties, 162–163
  compared with other agents, 170–171
  detectability by odor, 170
  detection and analysis, 163
  food and water poisoning, 171–172
  mechanism of action theories, 167–169
  physiological mechanism theories, 167–169
  rodenticide use, 172
  stability, 162–163
  synthesis and properties, 156
Methyl fluoroacetate toxicity, 163–170
  animal toxicity, 165–167
  chemical structure, relation to toxicity, 163–165
  death, 166–167
  human toxicity, 170
  inhalation toxicity, 166
  intravenous injection toxicity, 165
  latency in poisoning, 166
  oral toxicity, 165
  subcutaneous injection toxicity, 165
  therapy, 169
Methyl γ-fluorobutyrate, 161
Methyl γ-fluoro-β-hydroxybutyrate, 162
Methyl formate in diphosgene production, 21–22
Methyl-β-chloroethyl-β-hydroxyethylamine hydrochloride, 464–466
Methyl N-(β-chloroethyl)-N-nitrosocarbamate
  see Aliphatic nitrosocarbamate (KB-16)
Methyl-β-chloroethyl sulfide, 54
Meyer process for mustard gas, 30
Meyer reaction of aliphatic arsenicals, 85
MFI war gas
  see Isopropyl methanefluorophosphonate (MFI)
Microline gas chamber, 283
Micropipets for mustard gas tests, 53
Mineral oil deterioration of carbon-treated fabrics, 550
Miscellaneous compounds examined as chemical warfare agents (tables), 246–264
Miticides, 650
Mitosis inhibition by vesicants
  in mammalian cells, 437–438
  in marine eggs, 438

MMD (mass median diameter) of clouds, 272–275
aggregates, effect on MMD, 273–274
determined by cascade impactor, 272–274
determined by microscope examination, 272
effect on vesicant action, 274–275
nonspherical particles, 273
ricin clouds, 188–189
Molecular structure in relation to vesicancy, 505–507
Molecular structure of warfare agents, 620
Moorehouse's systemic hyperthermia studies, 309
Mucosal necrosis, 323
Munitions
see Bombs
Mustard gas
see also Nitrogen mustard gas; Sulfur mustards
analogues susceptible to photosynthesis, 43
evaluation for war use, 57–58
field tests, 79–80
man-chamber tests, 74–76
mixture with 1,2-*bis*(β-chloroethylthio) ethane, 30
mixture with *bis*(β-chloroethylthioethyl) ether, 30
organic sulphur analogues, 44–53
physical properties, 44, 67–81
solubility in water at room temperature, 68
susceptibility to; *see* Vesicant susceptibility factors
table of organic sulfur compounds, 45–52
thermal bombs, 57
vesicancy, 70–75
vesicancy tests, 53–56
water contamination, 624–625
Mustard gas compared with
aliphatic nitrosocarbamate (KB-16), 23, 130
1,2-*bis*(β-chloroethylthio) ethane (Q), 54
lewisite, 88–89, 92–94
Mustard gas detection, 581–583
DB-3 reagent, 581
detectable concentration, 69
detectable odor, 53
iodoplatinate test, 582
nitrogen mustards, 583
Spotted Dick test, 582
thiourea test, 582
Mustard gas determination, 602–604, 616–618
bromate-bromide thiosulfate titration, 604
bromine titration, 602
chloramine titrations, 602–603
DB-3 colorimetric method, 603
gold chloride-benzidine colorimetric method, 604
hypochlorite titration, 602
iodate thiosulfate titration, 604
iodoplatinate test, 605
mercurimetric titration, 603
β-naphthol turbidimetric method, 603
p-nitrobenzyl bromide colorimetric method, 604
pyridine colorimetric method, 603
pyrolytic recorder, 617–618
sensitized film recorder, 616–617
thiosulfate titration, 604
Mustard gas effect on enzymes and cells, 433–437
carcinogenesis, 437
corneal metabolism and loosening, 436
enzyme inactivation by mustards, 433–434
permeability, 437
Peters' enzyme hypothesis, 433–434
tissue cultures, 436–437
yeast metabolism and reproduction, 434
Mustard gas effect on nuclear activity, 437–439
chromosomal mechanisms, 437
mitosis in mammalian cells, 437–438
mitosis in marine eggs, 438
swelling inhibition, 438–439
Mustard gas of Levinstein type, 33–42
β-chloroethylsulfenyl chloride reaction, 40
composition theories, 33–34
contamination by iron containers, 39
effect of temperature on formation, 41
fractionation by hydrolysis, 35
hexamine stabilizer, 42
mechanism of formation, 40–41
methanol extraction, 34
minor impurities, 39
molecular distillation, 33
molecular weight of impurities, 37
properties of polysulfide constituents, 35–39
purification methods, 42
refractive indices of fractions, 37
Reid-Macy hypothesis of composition, 34–35
synthesis of polysulfides, 35
"trichloro mustard" impurity, 39
vacuum distillation, 42
Mustard gas pharmacology, 440–478
tris(β-chloroethyl)amine, 470–476
ethyl-*bis*(β-chloroethyl)amine, 457–460
isopropyl-*bis*(β-chloroethyl)-amine, 476
methyl-*bis*(β-chloroethyl)-amine, 460–470
nitrogen mustard related compounds, 476–478
(β-chloroethyl) sulfide, 442–454
(β-chloroethyl) sulfide related compounds, 454–457
summary, 442
Mustard gas production
French process, 30
Guthrie process, 30
"H" processes, 32
Levinstein process, 31–32
Meyer process, 30
photosynthetic method, 42–43
QP process, 30, 41
South African process, 32
Mustard gas reaction with proteins, 431–433
casein reactions, 432
*p*H dependency of reactions, 432
phenolic and indolyl groups, 432
protein properties altered by reaction, 432–433
sulfhydryl groups, 432
Mustard gas skin injury, 479–518
biochemical changes in vesicant treated skin, 499–502
factors determining effectiveness, 507–513
immunology, 502–505
molecular structure and vesicancy, correlation, 505–507
pathology of vesicant burns, 479–487
penetration of skin by mustards, 487–498
prevention, 513–518
summary, 479
treatment of skin, 515–518
Mustard gas systemic effects, 440–442
see also Mustard gas skin injury
blood constituent changes, 440–441
blood-forming organs, 441
cholinergic action, 441
convulsive action, 442
cytolytic action, 440–441
delayed death, 440
eye injuries, 56, 73, 78–79
neurologic injury, 442
parasympathetic action, 442
peripheral circulatory failure, 440
prophylaxis and therapy, 441
summary, injury in man, 441
toxicity in drinking water, 56–57
Mustard gas toxicology
see Mustard gas skin injury; Mustard gas systemic effects

N-182 National carbon, 539
N oxides of nitrogen mustards, 396–397

Naphthalene derivated carbamates, 240–241
β-Naphthol turbidimetric determination of mustard gas, 603
Nasal filtration in precisi.. gassing, 297–299
  filtration with corn oil, 298
  filtration with sodium bicarbonate, 298–299
  setting up particulate cloud, 297–298
Naval Research Laboratory, protective clothing test, 553–554
Negro skin, susceptibility to vesicants, 507–508
Neurological injury
  by methyl-*bis*(β-chloroethyl)-amine, 458
  by mustards, 442
Nickel carbonyl, 176–178
  as warfare agent, 178
  carbon monoxide release, 176–177
  inhalation vs. injection, 178
  parenteral administration, 177–178
  physiological action, 176–177
  summary, 178
  toxicity by inhalation, 177
p-Nitrobenzyl bromide colorimetric determination of mustard gas, 604
Nitrogen mustard compounds (tables), 60–65
  derivatives of primary amines, 60
  derivatives of quaternary ammonium salts, 65
  derivatives of secondary amines, 61–62
  derivatives of tertiary amines, 62–65
Nitrogen mustard gas, 50–82, 389–424
  see also Mustard gas
  chemical properties, 66
  decontamination, 68
  detection, 69, 583
  dimerization, 67
  evaluation as war gas, 80–82
  field tests, 79–80
  man-chamber tests, 74–76
  physical properties, 66–67, 81
  preparation, 59–66
  solubility in water at room temperature, 68
  stability in exploding shells, 67
  storage stability, 67
  structural formulas, 59
  susceptibility to; *see* Vesicant susceptibility factors
  terrain behavior, 68
  water contamination, 624
Nitrogen mustard gas, kinetics of reactions, 415–424
  β-chloroethylamines in heterogeneous systems, 423
  β-chloroethylamines in homogeneous solution, 416–423
  correlation of toxicities of β-chloroethylamines with kinetics of their cyclization, 423
  pH dependence of reactions, 415–416
  reaction mechanism, 415–416
Nitrogen mustard gas, reactions, 389–397
  tris(β-chloroethyl)amine (HN3), transformations in water, 392
  amino groups of amino acids and peptides, 394
  antinitrogen mustard agent, search for, 389
  carboxyl groups, 395
  cyclic amines, 394–395
  methyl-*bis*(β-chloroethyl)amine (HN2), hydrolysis in bicarbonate solution, 390–391
  methyl-*bis*(β-chloroethyl)amine (HN2), transformation in water, 389–392
  N oxides of nitrogen mustards, 396–397
  phosphates, 396
  secondary and tertiary aliphatic amines, 394–395
  sulfhydryl groups, 395
  summary, 396
  thiosulfate as reagent for ethylenimonium compounds, 391
  unbuffered aqueous solution behavior, 392–393
Nitrogen mustard gas, toxicology, 69–79
  tris-(β-chloroethyl)amine toxicity, 72
  anti-vesicant treatment, 72–73
  decontamination and treatment of eyes, 79
  effect of temperature and humidity, 70–72
  effect on animal eyes, 78
  effect on human eyes, 75–78
  ethyl-*bis*(β-chloroethyl)amine toxicity, 70
  methyl-*bis*(β-chloroethyl)amine toxicity, 71
  mortality data for animals, 69
  protection by ointment, 75
  protective clothing, 75
  summary, 69
  toxicity for animals, 69
  toxicity for humans, 70
  vesicancy, 70–75
Nitrogenous base reactions with sulfones and sulfoxides, 409–412
Nitrosocarbamates, aliphatic
  see Aliphatic nitrosocarbamate (KB-16)
NMD (number median diameter), 272
Northrup titrimeter electronic interval timer, 293–294
Northrup titrimeter test for protective clothing, 554–556
Nose penetration by particulate clouds, 275–276
Nuclear activity and vesicants, 437–439
  chromosomal mechanism, 437
  mitosis inhibition, 437–438
  swelling inhibition, 438–439
Nutritional deficiency and susceptibility to vesicants, 508–509

OCD detector kit, 587
Odor control with DDT, 646
Oil screening smokes, toxicity tests, 382–383
Ointments for vesicant protection, 525–528
  action of agent on vesicant, 527–528
  agents other than chloramides, 527
  CC-2 ointment, 527
  developmental ointments, 525–526
  duration of protection, 528
  M-5 ointment, 528
  requirements, 525
  S-330 ointment, 526–527
  S-461 ointment, 525
Osmoscope detection of phosgene, 20

Paints for detection of liquid warfare agents, 585–586
Pancreas secretions and (β-chloroethyl) sulfide, 447
Paper for detection use, 595
Paper tape recorder, 614–616
Paralytic action
  of cyanide poisoning, 15
  of methyl-*bis*(β-chloroethyl)-amine, 462
  of mustards, 442
Parasympathetic system affected by (β-chloroethyl) sulfide, 446–447
  gastric secretions, 447
  intestinal secretions, 447
  pancreas secretions, 447
  peripheral action, 446
  salivary secretions, 447
Parasympatholytic action of mustards, 442
Particles, toxic
  see Particulate clouds
Particulate clouds, 267–277, 292–298
  coagulation, 269
  dispersal of liquids and solutions, 271
  dispersal of solids, 271
  dispersibility, 276
  impingement of particles, 270
  in precision gassing experiments, 297–299
  nonspherical particles, 273

particle size relation to properties, 270
particle size relation to warfare characteristics, 267
retention in lungs, 269
sedimentation, 269
solid particles, 273
sternutators, 268
summary, 268
types of clouds, 268–269
Particulate clouds, sampling, 272–277, 292–296
aggregates of particles, present measuring difficulties, 273 274
atomizing impinger, 294 295
bubblers, 292 293
cascade impactor, 274, 274, 295–296
field sampling methods, 276 277
filters, 294
mass median diameter (MMD), 272–274
Northrup titrimeter electronic interval timer, 293–294
number median diameter (NMD), 272
optical methods of analysis, 272
particle diameter measurements, 272
particle fractionators, 295
precipitators, 294
summary, 267 268
thermal precipitator, 272
ultramicroscopic observations, 272
vapor concentration sampling, 292 294
volume median diameter (VMD), 272
Particulate clouds, toxicology, 267–271, 274–276
effective inhaled dose, 271
effective vesicant dose, 270 271
inhalation toxicity, 271, 276
nose penetration, 275 276
particle size, effect on vesicancy, 269, 274–275
summary, 267–268
vesicancy, 269, 274 275
wind speed effect, 270 271
Paste, DDT dispersible, 645
Pathology of warfare agents
see under name of individual agent
PD (phenyldichlorarsine), 95 97
Pectic acid salts, binder for carbon-treated fabrics, 538
Peptide reaction with nitrogen mustards, 304
Peroxide
as lewisite antivesicant, 84 85
oxidation of *bis*-(β-chloroethyl) sulfide, 429
Perspiration
and vesicant susceptibility, 512–513
deterioration of carbon-treated fabrics, 551
protection against hot air injuries, 358–359
Peters' hypothesis, enzyme reaction with vesicants, 433
PF-1 war agent
see Dimethyl fluorophosphate (PF-1)
PF-3 war agent
see Diisopropyl fluorophosphate (PF-3)
Phenolic groups of proteins, reaction with vesicants, 432
β-phenyl-β-chloroethylamine, 423
Phenyldichlorarsine (PD), 95–97
Phosgene, 17 23
advantages, 17
as a war gas, 19–21
bombs, 202
canister protection, 17
detection, 17
diphosgene, 21–23
liberated upon oxidation of DDT, 643
manufacturing hazards, 20
maximum safe concentration, 20
oxime, 243
physical properties, 17, 20
preparation, 17
respiratory injuries, 17–19
stability, 17
toxicity, 17–20
toxicity compared with other agents, 19–20, 26
Phosphates
see also Ethyl dimethylamidocyanophosphate
alkyl cyanoamidophosphate, 131, 140–141
Phosphorus compounds, 131 155
chemical reactions, 142–143
decontamination, 144
detection, 144 145
eye effects, 145 150
in mustard gas production, 30
pathology, 153–154
physiological mechanism, 155
preparation, 132 142
protection, 144, 151 155
skin effects, 154
stability, 143
structure, 131–132
table of all compounds studied, 133–137
toxicity, 176–154
Phosphoryl chloride method of synthesis of dimethyl fluorophosphate (PF-1), 138
Phosphoryl dichlorofluoride method of synthesis of dicyclohexyl fluorophosphate, 138
Phosphoryl fluoride, diamido
preparation, 139 140
structure, 131
toxicity, 132
Phosphoryl fluoride, *bis*(dimethylamido)
eye effects, 150
structure, 131
toxicity, 153
Photochlorination of methyl formate to diphosgene, 22
Photoelectric dosage meter, automatic, 619
Photosynthesis of mustard gas compounds, 42–44
Physostigmine, 204
Pigment differences, effect on susceptibility to vesicant, 507–508
Pillbox temperature after flame thrower attack, 304
Plant toxalbumins
see Ricin
Plasma exposure to (β-chloroethyl) sulfide, 442–444
Plasma potassium after cutaneous hyperthermia, 362–366
cell volume increase, 363–365
erythrocyte content of potassium, 365–366
experimental procedure, 362
extravascular diffusion, 363–365
in vitro effects of heat, 366–368
post mortem rise in plasma, 363
strangulation effects on blood, 363
summary, 368, 378
Plasma protein ratio (A/G), 445
Plasma turbidity after burning, 359–360
Polymerization of cyanogen chloride, 8
Polyvinyl esters as binders for carbon-treated fabrics, 538
Pope-Turner aromatic arsenical process, 80
Potassium content of plasma affected by heat
see Plasma potassium after cutaneous hyperthermia
Potentiometric dosage meters, automatic, 619
Powders
chloramide, 527
DDT dispersible, 644–645
for detection of liquid warfare agents, 586
Precipitators for particulate sampling, 294
Precipitin test for ricin, 197, 200
Precision gassing, 296–299
see also Gas dispersal into chambers
cloud passage through human respiratory system, 298–299

equipment, 296–297
inhalation toxicity of particulates, 297
intrapulmonary installation of agent, 297
mask, 296
nasal filtration with corn oil, 298
nasal filtration with sodium bicarbonate, 298 299
particle retention in human lungs, 299
particulate cloud formation, 297 298
valve system, 296 297
Procaine treatment of fluoroacetate poisoning, 169
Propulsion fuels
gasoline adjuvants for aeropulse motors, 639-640
hydrogen peroxide preparation, 640
hydropulse fuels, 634-640
Propyl-*bis*(β-chloroethyl)amine, 60
"Propyl mustard gas", 41
Protein
alterations after heat exposure, 351–353
binders for carbon-treated fabrics, 538
Protein reactions with vesicants, 431–433
casein reactions, 432
*p*H dependency of reactions, 432
phenolic and indolyl group reactions, 432
properties altered by reaction, 432
sulfhydryl group reactions, 432
Pumps for gas sampling, 597 598
compressed air injectors, 598
electric pump, constant-displacement, 598
electric pump, orifice-controlled, 598
liquefied gas injectors, 598
magnetic pump, 598 599
Pyrazolone-pyridine reagent for cyanogen chloride detection, 583
Pyridine, 4-(*p*-nitrobenzyl), for mustard gas detection, 53
Pyridine colorimetric determination of mustard gas, 663
Pyrolysis of mustard gas, 617-618
Pyrophosphatase activity affected by vesicants, 501
Pyruvate oxidation inhibition by vesicants, 501

Q war agent
see Ethane, 1,2-*bis*(2-chloroethylthio) (Q)
Quinoline derivated carbamates, 241–242

Racial differences, effect on susceptibility to vesicants, 507-508
Radiation, heat transfer role, 308
"Radiator effect" of body temperature, 512
Rayon-carbon fabrics, 545–548
see also Carbon-treated fabrics
carbon preparation, 545 546
evaluation, 547-548
knit fabrics, 546-547
weaving process, 546
yarn, 545
Red cell changes caused by (β-chloroethyl) sulfide, 445, 453
Reid-Macy mustard gas composition hypothesis, 34-35
Research recommendations
chloramide-impregnated clothing, 535
metabolic disturbances in poisoned animals, 191
ricin effect on unicellular organisms, 191
Respiratory damage from
aliphatic fluorine compounds, 166
aliphatic nitrosocarbamate (KB-16), 123–124
cadmium compounds, 174
carbonyls, nickel and iron, 177
cyanogen chloride, 12, 15
disulfur decafluoride, 27–28
exposure to gasoline conflagrations, 305-306
fluorophosphates and phosphorus compounds, 150–154
lewisite, 88, 90
methyl fluoroacetate, 166
particulate clouds, 271, 275–276
phosgene, 18, 20
retention of toxic particles in lungs, 299
ricin, 188 190
selenium dioxide, 175
toxic particles retained in lungs, 299
Respiratory damage from heat, 320-325
alveolar ducts and alveoli injury, 323
amount of heat in one breath, 323
cutaneous hyperthermia effects, 375–376
experimental procedure, 320
fluctuations in respiratory rate, 375-376
inhaled air, rate of cooling, 320-322
larynx protection, 322-323
mucosal necrosis, 323
primary thermal injury of lungs, 323
skin vs. respiratory tract, amount of heat transfer, 323 325
summary, 325
water content of inhaled gas, 324
Respiratory measurements during gassing
see Precision gassing
RH-195/TCE decontaminating system, 573–574
Ricin, 179–203
as war gas, 201, 203
clouds, 188-189
detection, 196–198
enzyme activity, 191
mechanism of action theories, 190–191
sodium sulfate cake, 185–186
summary, 179, 203
Ricin, amorphous, 181–183, 185–187
castor beans, raw material, 181
comminution, 182-183
preparation B1; 186
preparation 470 2M 199; 186
preparation L703; 186
properties, 181
ricin-sodium sulfate cake, 185-186
toxin extraction from bean meal, 181–182
toxin isolation from aqueous extract of pomace, 182
Ricin, crystalline
chemical composition, 180
preparation, 180–181
properties, 180
Ricin assay, 197-201
bioassay, 198–199
chemical assay methods, 200–201
dose-survival time curve for mice, 199-200
enzyme activity, 200
field detection, 201
hemagglutination, 197, 200
molecular homogeneity of ricin not determined, 198
precipitin method, 197 200
Ricin bomb dispersion
carbon tetrachloride vs. water suspension, 202
comparison with phosgene bombs, 202
ejection bombs of dry ricin, 201–202
explosive bombs of suspended ricin, 201-202
plastic bombs, 202
Ricin immunology, 191 198
active immunization of animals, 195-196
antiserums, 193-194
human immunization, 196
immunological methods for ricin detection, 196 198
program summarized, 191-192
therapeutic use of antiricin, 191
toxoids, 192 193

Ricin preparation, 183–185
cost of production, 183
extraction, second time, 184
extraction of pomace, 183
precipitation and filtration, first time, 184
precipitation and filtration, second time, 184
spray drying and air grinding, 185
starting material, 183
summary, 179–180
Ricin toxicity, 187–190
anaphylactic responses of sensitized animals, 197–198
as a cloud, 268
eye damages, 188–189
human toxicity, 189–190
inhalation toxicity, 188–190
intoxication symptoms, 189
parenteral toxicity, 187–188, 190
particle size distribution of toxin, 188–189
relation of survival time and dose, 188
Rodent control, 641–650
DDT, 641–646
methyl fluoroacetate, 172
red squill powder, 650
rodenticides, 650
sodium fluoroacetate, 172
Rods for vesicant testing, 300–301
Benesh micropipet, 300–301
Drods, 299–300
Edgewood rods, 299
Rubber latex carbon-treated fabrics, 537, 540–541, 549–550
Rydon theory, applied to decomposition of *bis*-(β-chloroethyl) sulfide, 405

S-210 impregnite for vesicant detoxification, 523
S-328 impregnite for vesicant detoxification, 522
S-330 impregnite for vesicant detoxification, 521, 523–524
S-330 protective ointment, 526–527
deterioration of carbon-treated fabrics, 550
treatment for mustard gas injury, 75
S-430 impregnite for vesicant detoxification, 521
S-461 impregnite for vesicant detoxification, 522–523
S-461 protective ointment, 526
Salicomine dusts, 383–384
animal exposure effects, 384
human exposure effects, 384
prolonged exposure effects, 384
structure, 383
Salicylaldehyde ethylenediimine cobalt, 383
Salivary secretions and (β-chloroethyl) sulfide, 447
Sampling equipment for toxicological studies, 292–296
see also Field sampling procedures
absorber, 293
atomizing impinger, 294–295
cascade impactor, 295–296
filters, 294
Northrup titrimeter, 293–294
particulate sampling, 294–296
precipitators, 294
vapor concentration sampling, 292–294
"SB substances", methyl-*bis*(β-chloroethyl)-amine effects, 460–461
Schiemann's fluorine reactions, 631
Screening smoke chamber, 281–282
Screening smoke toxicity tests, 382–383
Selenium
as warfare agent, 175–176
physiological action, 175
selenium oxide smoke, 175–176
summary, 173
toxicity by inhalation, 175
Sensitization of skin to vesicants
see Cutaneous sensitization to vesicants
Sesquimustard, 456–457
Shells, cyanogen chloride charged, 10
Shells, high-explosive chemical, 68
Silica gel vapor detectors, 584–585
Silver's equation, chamber equilibration times, 278
60P mustard gas process, 30
Skin, human vs. porcine, 325–329
blood vessels, porcine, 327–328
dermis, 326–329
epidermis, 325–326
pathological response to vesicants, 482–483
relative vulnerability to thermal injury, 333–334
summary, 329
sweat glands, 328–329
Skin burns
see Cutaneous burns; Heat transfer to skin
Skin toxicity of
aliphatic nitrosocarbamate (KB-16), 124
cyanogen chloride, 15
fluorophosphates, 154
lewisite, 87–88, 90–92
mustard gas, 479–518
(β-chloroethyl) sulfide, 452–453
Smokes, toxic
arsenical irritant, 112–114
cadmium oxide smokes, 171–175
identification kit, 593
microdine smoke chamber, 283
oil smokes, 382–383
screening smoke chambers, 281–282
selenium oxide smoke, 175–176
Soap deterioration of carbon-treated fabrics, 550–551
Sodium acetate treatment of fluoroacetate poisoning, 169
Sodium *p*-aminobenzoate treatment of fluoroacetate poisoning, 169
Sodium bicarbonate, nasal filtration use, 208–209
Sodium fluoroacetate
rodenticide use, 172
synthesis, 156–161
Sodium pyrophosphate as cyanogen chloride stabilizer, 10
Sodium thiosulfate as preventative for methyl-*bis*(β-chloroethyl)-amine injuries, 464–466
Spectroscopic analysis of DDT, 642–643
Spotted Dick, mustard gas detection test, 582
Spotted Dick, protective clothing test, 553
Starling and Knowlton's heart hyperthermia studies, 309
Steady-state heat conduction equation, 308–309
Steam, heat injury production, 308
Sternutators, 268
Strangulation from cutaneous hyperthermia, 363
Sulfhydryl group reactions
with nitrogen mustards, 395
with sulfones and sulfoxides, 409
with vesicants, 432
Sulfide ethers examined for war use, 45–47
Sulfides
see also Sulfides, β-chloroethyl; Sulfides, *bis*(β-chloroethyl); Sulfur mustards
bis(β-bromethyl) sulfide, 54
alkyl β-chloroethyl sulfides, 412–413
aryl β-chloroethyl sulfides, 412–413
benzyl β-chloroethyl sulfides, 54, 490
ethyl β-chloroethyl sulfides, 54, 490
methyl β-chloroethyl sulfides, 54
β-chloroethyl β-chlorovenyl sulfides, 39
β-chloroethyl β-hydroxyethyl sulfides, 406, 454
1,2,2'-trichlorodiethyl sulfides, 39
Sulfides, β-chloroethyl, 442–454
atropine-like effect, 446
bile elimination from intestine, 450
capillary permeability, 450
cross-transfusion experiments, 451
deaths from systemic injury, 453–454
excretion effects, 442–444
gastric secretion effects, 447

human intoxication effects, 452–454
intestinal secretion effects, 447
intravenous injection effects, 452
magnesium-sensitized animals, 450
pancreas secretion effects, 447
parenteral toxicity, 443
penetration and distribution in system, 442–444
peripheral action, 446
prophylaxis and therapy, 448–449
salivary secretion effect, 447
sensitization, 450
skin contamination, 452–453
systemic action, summary, 444–445, 451–452
tissue action, 450
urine effects, 453
vomiting effect, 447
vomiting effect, temperate vs. tropic climates, 452
water and electrolytic metabolism effects, 447–448
Sulfides, (β-chloroethyl), effect on blood, 444–446
albumin-globulin plasma protein ratio, 445
anemia, 445
coagulation time, 453
electrophoretic pattern, 445
hemoconcentration, 445
leucopenia in men, 453
lipemia, 450
miscellaneous effects, 446
NPN (non-protein nitrogen) rise, 445–446
occlusion of blood supply, 449
plasma concentration changes, 442–444
red cell count changes, 445, 453
Sulfides, *bis*(β-chloroethyl), 397–405
see also Mustard gas
activation process, 400
alkylation reactions, 400
amine reactions, 404–405
carboxyl group reactions, 401–404
"competition factors", 400–401
detoxicants; *see* Chloramides for vesicant detoxification
oxidation by peroxides, 420
preparation, 30
pyridine reactions, 401
Rydon decomposition theory, 405
stability of derivatives, 405
sulfide sulphur reactions, 401
sulfonium salts formed during hydrolysis, 398–400
thiodiglycol (TG) esters, formation, 404
transformations in water, 397–400
Sulfinic and sulfonic acid derivatives examined for war use, 45–52
Sulfone II, 408–412
nitrogenous base reactions, 409–410
pharmacology, 456
sulfhydryl group reactions, 409
summary, 412
water reactions, 408
Sulfones and sulfonium salts examined for war use (tables), 45–52
Sulfones and sulfoxides, chemical reactions, 408–412
nitrogenous base reactions, 409–412
sulfhydryl group reactions, 409
summary, 412
water reactions, 408–409
Sulfonium compounds
see also Ethylenesulfonium; Sulfones
tris(β-chloroethyl) sulfonium chloride, 406
β-chloroethyl β-[*bis*(β-hydroxyethyl) sulfonium]ethyl sulfide chloride, 454
bis[*bis*(β-hydroxyethyl) sulfonium-ethyl] sulfide dichloride, 456
Sulfoxide II, 408–412
pharmacology, 456
summary, 412
water reactions, 409
Sulfoxides examined for war use (tables), 45–52
Sulfur compounds as warfare agents, summary, 45–52
Sulfur dichloride processes for mustard gas, 32
Sulfur fluorides, calculated equilibria, 25
Sulfur hexafluoride, 24–25
Sulfur monochloride for mustard gas production, 32
Sulfur mustards
effect on enzymes and cells, 435
general properties; *see* Mustard gas
in heterogeneous systems, 429–430
table of compounds, 45–52
Sulfur mustards in homogeneous solution, 424–429
ethylenesulfonium ion formation, 424–425
ethylenesulfonium ion kinetics, 425–427
ethylenesulfonium ion reactions, 427–428
kinetics of oxidation of *bis*(β-chloroethyl) sulfide (II) by peroxides, 420
kinetics of reaction mechanism, 415–416
reaction formulation, 424
reaction kinetics, 428–429
bis(β-chloroethyl) sulfide in aqueous solution, 425–426
Sulfur tritadichloride in mustard gas formation, 40
Summary, all compounds examined as chemical warfare agents, 3–6, 247–264
Summary of work of Div. 9, NDRC, 3–6
Sweat glands, porcine vs. human, 328–329
Sweating
deterioration of carbon-treated fabrics, 551
effect on vesicant susceptibility, 512–513
protection against hot air injuries, 358–359

Tactical factors in poison gas use, 7, 23
Tape recorders, 614–618
paper tape recorder, 614–616
pyrolytic mustard gas recorder, 617–618
sensitized film for mustard gas recorder, 616–617
Temperature, concept of, 307
Tetrazobenzenesulfonate, 404
Tetrachloroethane
solvent for carbon-impregnated clothing, 540
solvent for chloramide-impregnated clothing, 529
TG war agent
see Thiodiglycol (TG)
Therapeutic agent, BAL, 94–95, 570–571
BAL glucoside, 571
chemical analogs, 571
Peters' hypothesis, 433–434
synthesis, 570
Thermocouple
determining surface temperature of skin, 314–315
determining tissue temperature beneath sites of cutaneous exposure, 313–314
Thiocid derivatives examined for war use (table), 50–51
Thiocarbazone reagents for arsenical detection, 582
Thiodiglycol (TG)
dinitrate, 404
esters, 404
pharmacology, 454
production processes, 30
sulfone, toxicity in drinking water, 57
sulfoxide, toxicity in drinking water, 57
use in mustard gas production, 30–31
Thionyl chloride for mustard gas production, 30
Thionyl chloride in nitrogen mustard preparation, 59

Thiosulfate as reagent for ethyleniminonium compounds, 391
Thiosulfate preventative for methyl-*bis*(β-chloroethyl)amine, 464-466
Thiosulfate titration of mustard gas, 604
Thiourea test for mustard gas, 582
Thymus hemorrhages from cyanide poisoning, 15
Tissue changes after heat exposure
see Cutaneous tissue changes after burns
Tissue cultures, vesicant exposure effects, 436-437
Tissue heat conductivity
see Heat transfer to skin
Titrimeters, 609-614
automatic, 611 614
electrolytic, semiautomatic, 610-611
electrolytic recording, automatic, 612-614
field model, electrolytic semiautomatic, 610 611
field model, semiautomatic, 609-610
mustard gas use, 53
Northrup, 203 204
recording, automatic, 612-614
semiautomatic, 608 611
TL toxic agents, 205 207
see also Aromatic carbamates
TL 599; 206
TL 1071; 205-206
TL 1216; 206
TL 1217; 205, 207
TL 1299; 205, 207
Toxicity of warfare agents
see under name of specific agent
Toxicological Research Laboratory, CWS, 11
Toxicological study apparatus, 278-302
dispersal apparatus, gas into chambers, 285 292
gassing chambers, 278 285
"precision gassing" equipment, 286-289
sampling equipment, 292 296
vesicant testing equipment, 299 300
Transepidermal necrosis
see Cutaneous burns
1,2,2'-trichlorodiethyl sulfide in mustard gas, 39
Trichloromethyl chloroformate
see Diphosgene
Trichloromustard impurity in mustard gas, 32
Triethylaluminum triethylboron mixtures, 636
Tribus, German war gases
alkyl cyanoamidophosphates, 140-141
alkyl fluorophosphonates, 141-142
structure, 131-132
Tropical conditions for sampling
see Field sampling procedures
TU (toxicity unit), ricin lethal dose, 198 199
Typhus control with miticides, 650

Ultraviolet spectroscopy for DDT determination, 643
University of Chicago Toxicity Laboratory
aromatic carbamate testing, 207-208
metals as toxic agents, 173-178
toxicological apparatus, 278-302
Urea intravenous injections, 448
Urea peroxide, lewisite antivesicant, 84-85
Urine, effects of (β-chloroethyl) sulfide on, 453
Uyeno's systemic hyperthermia studies, 368 369

V-1 buzz bomb fuel, 659
Valve systems in precision gassing, 286-287
Vapor detection, 584-587
see also Detection of warfare agents
British detector kit, 586
M-9 vapor detector kit, 586
Navy Mark 1 detector kit, 587
Vapor pressure of warfare agents, 20, 626
Vapor sampling, 292-295, 594-600
absorber, 293
bubblers, 292 293, 599 600
dosage determination, 594 600
Northrup titrimeter electronic interval timer, 293-295
pump units, 597-599
sampling installations, 597
sampling periods, 595-596
sampling points, 594-595
vesicant testing device, 301-302
Vesicant action
see also Cutaneous burns from vesicants
of aliphatic nitrosocarbamate (KB-16), 125-126
of heat on skin, 345-346
of mustard gas, 53-56, 73
of nitrogen mustard gases, 70 75
of phosphorus compounds, 154
Vesicant action of particulate clouds, 269 275
effective dose, nonvolatile vesicant, 270 271
homogeneous vs. heterogeneous cloud doses, 270
particle size, effect on vesicancy, 269, 274 275
volatile vs. nonvolatile vesicants, 269
wind speed effect, 270 271
Vesicant detoxification
see Chloramides for vesicant detoxification
Vesicant immunology, 502-505
degree of hypersensitivity, 504
desensitization, 505
guinea pig sensitization, 503-505
human sensitization, 502-503
induction of hypersensitivity, 503-504
onset time of hypersensitivity, 504
prevention of sensitization, 504-505
sensitivity to vapor, 503
serum protein complexes, 505
susceptibility, normal vs. sensitized animals, 504
Vesicant reactions with proteins, 431-433
casein reactions, 432
pH dependency of reactions, 432
phenolic and indolyl group reactions, 432
protein properties altered by reaction, 432
sulfhydryl group reactions, 432
Vesicant susceptibility factors, 507-513
age, 508
amount of exposed skin, 512
clothing, 512
[illegible]ing 509
dosage of vesicant, 510
exposure time, 510
humidity, 511
mixtures of vesicants, 510-511
nutritional state, 508-509
part of body, 508
pigment differences, 507-508
racial differences, 507-508
seasonal differences, 509
state of vesicant, 509
sweating, 511-513
temperature of surroundings, 511
variations among individuals, 508
wind velocity and airflow, 511 512
Vesicant testing equipment, 299 302
Beresh micropipet, 300 301
Draves, 299-300
dynamic chambers for body exposure, 302
Edgewood rods, 299
Edgewood vapor cups, 301
liquid vesicant cup, 301
vapor train, 301 302
wind tunnels, 302
Vesicants
see Mustard gas; Nitrogen mustard gas
Vinyl chloride for mustard gas production, 12

Viscose coating of carbon-treated fabrics, 544
VMD (volume median diameter), 272
Volume inhaled per breath, 12
Vomiting caused by (β-chloroethyl) sulfide, 417
Vomiting in temperate vs. tropic climates, 452

W toxic agent
  see Ricin
War gases
  arsenicals, 83–114
  carbamates, aromatic, 204–245
  carbonyls, 176–178
  cyanogen chloride, 7–16
  diphosgene, 21–23
  fluorine compounds, 23–29
  fluorine compounds, aliphatic, 150–172
  fluorocarbons, 629–633
  fluorophosphates, 131–155
  hydrogen cyanide, 7–16
  miscellaneous compounds, 245–264
  nitrogen mustards, 59–82
  nitrosocarbamates, aliphatic, 115–130
  phosgene, 17–21
  ricin, 179–203
  sulfur mustards, 30–58
  summary, 3–6
Water burns, 357
Water contamination, 624–626
  aliphatic nitrosocarbamate (KB-16), 125
  analysis of water, 625
  arsenicals, 625
  cyanogen chloride, 625
  fluorine compounds, 171–172, 625
  methyl fluoroacetate, 171–172
  mustard gas, 56–57, 624–625
  nitrogen mustards, 124
  testing kit, 587
  treatment of water, 625–626
Wind tunnels
  for area exposure studies, 284–285
  for vesicant testing, 302
Wind velocity and vesicant dispersal, 270–271, 511–512

Yeast after exposure to vesicants, 434–436
  metabolism effects, 434
  morphological abnormalities, 434
  reproductive defects, 434

Zinc sulfate-molybdic acid test for arsenicals, 582

CLASSIFICATION CHANGED TO
UNCLASSIFIED

PTS 1-2 AD-234270 PTS-3-4 AD-234249 ~~SECRET~~ Unclassified

ATI- 30806

TITLE: Chemical Warfare Agents, and Related Chemical Problems - Parts I-II-III-VI
Vol. 1

AUTHOR(S): Moore, S.; Gates M.; Renshaw, R.; and others

ORIGINATING AGENCY: Office of Scientific Research and Development, NDRC, Division 9

PUBLISHED BY: (Same)

REVISION: (None)

ORIG. AGENCY NO.: (None)

PUBLISHING AGENCY NO.: (Same)

DATE	DOC. CLASS.	COUNTRY	LANGUAGE	PAGES	ILLUSTRATIONS
1946	Secr.	U.S.	Eng.	812	photos, tables, diagrs, graphs

ABSTRACT:

Preparation and evaluation of potential chemical warfare agents are described. Special physiological and toxicological studies including the assessment of particulates as chemical warfare agents, apparatus and techniques utilized in toxicological studies, and physiological mechanisms concerned in the production of casualties by exposure to heat are discussed. Physiological mechanisms of action of the sulfur and nitrogen mustards and protection against chemical warfare agents are considered. The investigations have demonstrated that the sulfur and nitrogen mustards are potent and relatively nonspecific alkylating agents. Detection and analysis of chemical warfare agents and other miscellaneous investigations are included.

S to U and c/2 to A/1 per OSRD ltr dtd 10 May 1966

DISTRIBUTION: Copies of this report obtainable from Air Documents Division; Attn: MCIDXD

DIVISION: Ordnance and Armament (22)
SECTION: Chemicals and Incendiaries (11)

SUBJECT HEADINGS: CW (28240); Research - Summary reports (81658.95)

ATI SHEET NO.: S-22-11-14