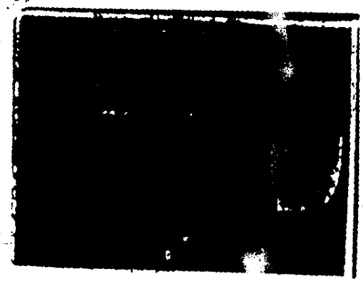
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MEDICAL DEPARTMENT, UNITED STATES ARMY

INTERNAL MEDICINE IN WORLD WAR II

Volume II

INFECTIOUS DISEASES

Prepared and published under the direction of
Lieutenant General LEONARD D. HEATON
The Surgeon General, United States Army

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INFECTIOUS DISEASES

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Foreword

This volume, the twenty-first to be published in the total series relating the history of the United States Army Medical Department in World War II, is the second volume to be published in the internal medicine group. The first volume, published in 1961, dealt with the activities of consultants in medicine in all parts of the world. This second volume deals with some of the infectious diseases encountered in a global war. The third and final volume in this group, now in preparation, will deal further with the infectious diseases and with general medicine.

Of necessity, as the editor of the internal medicine group points out in his preface, some of the material in this volume overlaps some of the material in the first internal medicine volume. It also overlaps certain of the material in the preventive medicine series. There has been, deliberately, no effort to alter the situation. To do so would have resulted in rigid and artificial distinctions and would also have deprived the reader of the benefit, in certain instances, of presentation of material on the same subject from more than one point of view.

As I read this book in manuscript, I was impressed with a number of considerations, some peculiar to this volume, some shared by the other volumes. Let me list some of them:

1. The wisdom of our policy of utilizing the personal experiences of present and former medical officers, who, as has been repeatedly pointed out, not only helped to create but also to record the data upon which this whole history is based. The authors of the various chapters in this volume were selected to write them not only because of their eminence in their particular fields but also because they had had wartime experiences in these fields. More valid sources could scarcely be imagined.

2. The expansion of knowledge of the etiology, clinical picture, control, and management of certain diseases about which little—in some instances nothing—was known before the war. The list is incomplete but, as examples, one might mention sandfly fever; Q fever; scrub typhus; Brill's disease; primary atypical pneumonia; and cutaneous diphtheria.

3. The remarkable utilization of opportunities for investigation and the amazing amount of valuable data that emerged from these studies, which were often made under almost intolerable conditions, both in and out of combat. In addition to studies involving United States military personnel, including released prisoners of war, were the studies involving Recovered Allied Military Personnel; enemy prisoners of war; and, civilians.

In this connection one is impressed with the importance and value of the work done by the various boards, commissions, and subcommissions appointed to investigate, and recommend action upon, certain aspects of infectious diseases. Their investigations included acute respiratory disease; influenza and other epidemic diseases; typhus; neurotropic virus diseases; hemolytic streptococcal infections; airborne infections; tuberculosis; and malaria. When one realizes that some 15,000 drugs for the suppression and treatment of malaria were investigated, some cursorily and some definitively, during the course of the war, one can also realize the fruitless activities and actual chaos which might have resulted without the guidance of the Board for the Coordination of Malarial Studies.

4. The changing concepts of certain diseases and their management. In 1941, for example, no one would have dreamed that one of the most significant chapters in a volume in the internal medicine series of the history would concern venereal disease. In December 1943, the treatment of patients hospitalized with venereal disease ceased to be a responsibility of the genitourinary service and became a responsibility of the medical service in Army hospitals. Hospitalization then gave way to ambulatory treatment. In the case of syphilis, therapy evolved from the time-honored but cumbersome and hazardous methods with arsenicals and bismuth—impractical even under relatively static conditions of training and completely impractical in combat—to the resolute decision to use penicillin for this purpose. This decision, made by The Surgeon General and applied Army-wide even at a time when last-minute preparations for D-day in Europe were being made, solved a serious problem with greatest effectiveness. Trained manpower was conserved; channels of evacuation were not clogged by this type of patient; and, many hospital beds were freed for more urgent purposes. Further, the use of penicillin simplified the treatment of gonorrhea and reduced the complications arising from that disease from 23 percent in 1937 to 1 percent in 1944.

The spread of knowledge of all these diseases required almost "evangelical efforts" on the part of the medical consultants and others responsible for the training and indoctrination of medical officers. As to the troops, control of disease was a matter of individual indoctrination and to be effective required firm command support. Education concerning malaria and its suppressive management did not succeed until Atabrine discipline became an actuality. Then malaria rates fell from as high as 1,500 to 2,000 per thousand per annum, or higher, to negligible figures.

A careful reading of this book makes clear that if these diseases had not been controlled, the United States could have suffered a great military disaster without regard to enemy capabilities. Some of the authors frankly acknowledge that luck played a part in the happy outcome, and so it did. The epidemic of encephalitis did not occur on Okinawa until the island had been occupied, though sporadic fighting was still going on and troops were staging for the invasion of Japan. On the other hand, the Medical Corps can justifiably assume credit for its brilliant work in a number of these dif-

ferent diseases. Epidemic typhus was rampant in civilian populations with which many troops were in close contact, but there were only 104 cases in the United States Army and not a single death.

One or two comparisons with World War I figures are further proof of the improvement of medical management of infectious diseases in World War II: In World War I, 46,640 deaths, 73 percent of all deaths from disease, were caused by influenza, lobar pneumonia, bronchopneumonia, bronchitis, and measles. In World War II, in an Army over twice the size of the World War I Army and mobilized over a longer period, there were only 1,285 deaths from these causes. In World War I, tuberculosis was the leading cause of disability separations; it accounted for 11.1 percent of all separations and for 13.5 percent of all separations from disease. In World War II, tuberculosis was thirteenth in the list of disability separations and it was responsible for only 1.9 percent of separations for disease.

The primary mission of the Army Medical Service is to conserve and maintain the fighting strength of the Army. After the difficult struggle for Buna-Sanananda in the New Guinea campaign, largely because of the ravages of disease, the 32d Infantry Division had to be taken out of the line for rest and rehabilitation and it was ineffective for many months. Extrapolation of these facts and others makes clear what might have happened had such situations continued. It is to the everlasting credit of the Medical Department—supported by understanding line commanders—that they did not.

In retrospect, the Medical Department seems to have accomplished an almost impossible task. It made its mistakes, and, to speak bluntly, some of them should not have been made. What one of the authors of this book said of malaria might well be said of a number of other diseases, that the stages of education in it were painfully alike in all theaters and areas. Nonetheless, medical personnel conquered and held in check diseases that were bewildering in both kind and number; that offered multiple difficulties of diagnosis and differential diagnosis, particularly in their very early stages; and that sometimes were completely unknown and sometimes had been modified by environment and by the changes in the clinical picture that occurred when non-immune persons entered areas of endemicity.

As a surgeon, I, as well as many of my surgical confreres, have had to concentrate on the essential character of our specialty in dealing with combat casualties. In my role as The Surgeon General of the Army, my outlook is necessarily wider and my appreciation of this book is therefore much deeper.

Quite properly, since our task is the preparation of a history of the Army Medical Department in World War II, the chief emphasis in this book is upon the enormous clinical military experience with infectious diseases in all parts of the world. That does not make the volume less valuable as a text on these diseases for medical students, general practitioners, and specialists in internal medicine. I recommend it to them, as well as to medical officers of the Army and other armed services, as a compilation of data not readily come by elsewhere.

The nineteen authors of this volume deserve the grateful thanks of the Army Medical Service and of the medical profession in general. For a variety of reasons, some beyond our competence, some due to our own culpability, the preparation of these and other volumes of the history has been long delayed. It is a tribute to the sense of professional duty and the patriotism of these former medical officers that in the midst of their busy civilian lives they have added to their wartime service by taking the time to set down this record, and to carry out the task with real enthusiasm. That is evident on every page.

It is therefore my pleasure to express my gratitude to the authors of this volume and to its editor, Dr. W. Paul Havens, Jr., and to the Advisory Editorial Board of which Dr. Garfield G. Duncan is Chairman, for a mission well accomplished. It is my equal pleasure to express my appreciation to the personnel in my own office who are doing the prodigious work of producing these volumes.

LEONARD D. HEATON,
Lieutenant General,
The Surgeon General.

Preface

This is the second volume of the history of internal medicine in World War II. In the preface of the first volume, which contains the reports of the medical consultants, is recounted the story of the development of the organization that ultimately produced the history. Attention was called to the early enthusiastic efforts of Brig. Gen. Hugh J. Morgan and Colonels Walter Bauer, John S. Hunt, and Francis R. Dieuaide to implement its writing and to the subsequent formation of the Advisory Editorial Board, early in 1952, under the chairmanship of Dr. Garfield G. Duncan and under the overall direction of Col. Calvin H. Goddard, MC, then Editor in Chief of the history of the "Medical Department, U.S. Army, in World War II" and Director, The Historical Unit, U.S. Army Medical Service. An editorial office was established at The Jefferson Medical College of Philadelphia, and Dr. W. Paul Havens, Jr., of that institution, was made Editorial Director. Col. John Boyd Coates, Jr., MC, succeeded Colonel Goddard as Editor in Chief of the history and Director of The Historical Unit.

This volume is concerned with the clinical descriptions of certain infectious diseases and brings into sharp focus their impacts on military activities under a variety of circumstances in many different parts of the world. Viral, rickettsial, bacterial, and protozoal infections are discussed, and these chapters constitute a record of the great and unique experience of our Armed Forces with a variety of infectious diseases in a small block of time. The chemotherapeutic triumph of the sulfonamides in meningococcal infections is recorded here. The great diversity of effects of various infections on military activities is described, ranging from the relatively unimportant role of neurotropic virus diseases to the vast loss of time caused by respiratory diseases, sandfly fever, and malaria. Again and again, in almost every chapter in this volume, appear the results of investigations initiated either by the Armed Forces or by the various commissions working under their aegis.

Of necessity, there is overlapping of the material contained in this book and in volume I. However, in contrast to the more general aspects of various medical problems described by the consultants in the first volume, the chapters in this book were based on the observations of many medical officers and were written by physicians directly concerned with the responsibilities for the care of patients and the clinical investigations of their diseases. These men, peers in their fields, were able to combine insight, judgment, and experience in such a way that the chapters in this book rank as outstanding records of clinical achievement. The lapse of more than 15 years between the experiences recounted here and their publication in this volume does not detract from their value or interest. Actually, much of this material has

long since appeared in our medical journals, but this book serves to bring it together in its proper relationship with place and time in history. The delay in publication is not unprecedented, since both the "Medical and Surgical History of the War of the Rebellion" and "The Medical Department of the United States Army in the World War" appeared several years after the termination of the Civil War and World War I.

For those who are concerned with military medical history, it is of interest to note that World War II was the first great conflict in which fewer of our troops died of disease than of battle injuries and wounds. In the Civil War, there were among Union troops approximately 360,000 deaths, and of these, about 225,000 were caused by various diseases. Among the Confederate troops, it was estimated that there were not less than 200,000 deaths, and of these, 150,000 were estimated to be due to diseases. Of further interest to the medical historian is the changing importance of various infections in military activity. Of the three volumes comprising the "Medical and Surgical History of the War of the Rebellion," one of them was devoted solely to the subject of the alvine fluxes while the other two were devoted, respectively, to statistics and clinical descriptions of malaria, typhoid fever, cerebrospinal fever, smallpox, and a number of other acute infections. This is also illustrated by comparison of the mortality recorded for respiratory diseases in "The Medical Department of the United States Army in the World War" and in this volume dealing with World War II.

The editor wishes to express his sincere thanks to the countless medical officers who made the material for these chapters available and to the distinguished authors who have written them. In addition, thanks are due to Dr. Duncan and the entire Advisory Editorial Board for their constant support and to Colonel Coates for his many courtesies and vigorous assistance. In particular, appreciation is expressed to Miss Eleanor S. Cooper, whose tireless and painstaking attention to the preparation and editing of these manuscripts was an invaluable aid in the compilation of this history.

The editor and the authors are also greatly indebted to Mr. E. L. Hamilton, Chief, Medical Statistics Division, Office of the Surgeon General, Mr. A. J. McDowell, Assistant Chief, and Mr. M. C. Rossoff, Assistant Chief, Statistical Analysis Branch, who not only provided essential data but also checked and reviewed all statistical information contained herein.

Finally, grateful acknowledgment is made to Miss Janie W. Williams, Chief, Publication Section, Editorial Branch, The Historical Unit, for performing the final publications editing and to Miss Rebecca L. Duberstein, Chief, Editorial Section, Editorial Branch, The Historical Unit, for preparing the index for this volume.

W. PAUL HAVENS, JR., M.D.

Contents

		Page
FOREWORD		XI
PREFACE		XV
Chapter		
I	Respiratory Diseases (*Yale Kneeland, Jr., M.D.*)	1
	General Considerations	1
	Part I. Acute Respiratory Diseases	
	Common Upper Respiratory Infection	2
	Influenza	9
	Primary Atypical Pneumonia	16
	Bacterial Pneumonia	26
	Measles	32
	Mumps	35
	Infectious Mononucleosis	38
	Rubella	41
	Part II. Chronic Respiratory Diseases	
	Chronic Bronchitis	42
	Bronchiectasis	44
	Lung Abscess	45
	Spontaneous Pneumothorax	46
	Pulmonary Fibrosis	47
	Pulmonary Emphysema	48
	Malignant Disease of the Lungs	48
II	Sandfly Fever (*William A. Reilly, M.D., Roberto F. Escamilla, M.D., and Perrin H. Long, M.D.*)	49
	Etiology	52
	Epidemiology	53
	Immunity	55
	Clinical Course and Diagnosis	56
	Treatment and Prevention	57
	Summary	57
III	Dengue (*Richard B. Cappe, M.D.*)	59
	Introduction	59
	Incidence	60
	Specific Outbreaks	60
	Clinical Manifestations	71
	Scientific Investigations	76

Chapter		Page
IV	Neurotropic Virus Diseases (*John R. Paul, M.D.*)	79
	The Arthropodborne Virus Encephalitides	79
	Poliomyelitis	91
	Lymphocytic Choriomeningitis	99
	Rabies	101
V	Q Fever (*Charles A. Ragan, Jr., M.D.*)	103
	Occurrence	103
	Clinical Features	106
	Epidemiology	108
VI	Scrub Typhus (*Chris J. D. Zarafonetis, M.D., and Myles P. Baker, M.D.*)	111
	Clinical Experience	112
	Pathology	132
	Laboratory Aids in Diagnosis	133
	Specific Treatment	136
	Postwar Studies	138
	Summary	139
VII	The Typhus Fevers (*Chris J. D. Zarafonetis, M.D.*)	143
	Part I. Epidemic Typhus	
	Epidemiology	143
	Clinical Experience	145
	Pathology	169
	Development and Use of Laboratory Aids in Diagnosis	179
	Treatment	192
	Part II. Brill's Disease	
	Historical Note	201
	Epidemiology	202
	Clinical Picture	202
	Diagnosis	202
	Part III. Endemic (Murine) Typhus	
	Epidemiology	204
	Clinical Experience	205
	Laboratory Aids in Diagnosis	213
	Part IV. Summary	
	Epidemic Typhus	215
	Endemic (Murine) Typhus	221
	Epilogue	223
VIII	Rheumatic Fever (*Lowell A. Rantz, M.D.*)	225
	Epidemiology and Statistics	228
	Clinical Picture	229
	Early Treatment and Course	232
	Late Treatment and Results	233
	Reconditioning	235
	Disposition	236
	Control	237
	Research	238
	Summary	238

Chapter *Page*

IX Meningococcal Infections (*Worth B. Daniels, M.D.*) 239
Historical Note 239
Incidence During World War II 241
Pathogenesis 244
Meningococcal Bacteremia 244
Fulminant Meningococcal Bacteremia 249
Meningococcal Meningitis 256
Complications 258
Other Meningococcal Infections 259
Laboratory Diagnosis 260
Treatment 261
Pathological Findings 270
Treatment of Meningococcal Infections 271
Discussion 273

X Cutaneous and Other Aspects of Diphtheria (*Averill A. Liebow, M.D., and John H. Bumstead, M.D.*) 275

Part I. General Aspects of the Military Problem

Incidence 275
Immunization 278

Part II. Tropical Ulcers and Diphtheria

Sources and Dissemination of Information 279
Morphology 284
Morphology in Relation to the Bacteriology of the Lesions 288
Methods of Diagnosis 293
Associated Clinical Findings 295
Relation to the Schick Reaction 296
Cutaneous and Extracutaneous Diphtheria 297
Complications 298
Treatment of Cutaneous Diphtheria 304
Cost of Cutaneous Diphtheria to the Army 307
Role of Cutaneous Lesions in the Spread of Diphtheria 308
General Considerations of Diphtheria in the Tropics 310
Association of Cutaneous and Nasopharyngeal Diphtheria in Military Units in the Tropics 312
Diphtheria Transmitted From Military To Civilian Populations 315

Part III. A New Hemolytic Corynebacterium in Man

Part IV. Use of Penicillin in Treatment of Diphtheria

Part V. Problems Remaining for Investigation

Part VI. Summary

Chapter		Page
XI	Tuberculosis (*Esmond R. Long, M.D.*)	329
	Part I. Tuberculosis in the Army	
	Historical Perspective	329
	Discovery of Tuberculosis Before Induction	331
	Discovery of Tuberculosis in the Army	333
	Incidence and Discharge Rates	334
	Part II. Occurrence in Oversea Areas	
	European Theater of Operations	339
	North African and Mediterranean Theaters of Operation	353
	South Pacific Area	357
	Southwest Pacific Area	360
	Western Pacific Base Command	362
	Middle Pacific	364
	China-Burma-India Theater	364
	Alaskan Department	365
	Latin American Area	366
	Middle East	366
	Far East	366
	Part III. Particular Aspects of the Disease	
	Extrapulmonary Tuberculosis	367
	Pleurisy With Effusion	370
	Spontaneous Pneumothorax	372
	Mortality From Tuberculosis	375
	Part IV. Hospitalization and Treatment in the Zone of Interior	
	General Principles of Evacuation	378
	Specialty Centers for Treatment	381
	Orientation and Rehabilitation	388
	Part V. Care of Recovered and Captured Prisoners of War	
	Recovered Prisoners of War	390
	Captured Prisoners of War	392
	Treatment Under the Military Government in Germany	397
	Part VI. Tuberculosis in British and Canadian Military Forces	
	Royal Navy	400
	Royal Air Force	402
	Canadian Army	403
	Part VII. Significance of Army Experience for Control of Tuberculosis	
XII	Diagnosis and Treatment of the Venereal Diseases (*Paul Padget, M.D.*)	409
	Historical Note	409
	Gonorrhea	410
	Nonspecific Urethritis	418
	Syphilis	418
	The Minor Venereal Diseases	430
	Induction of Individuals With Venereal Disease	433
	The Results	434

Chapter		Page
XIII	Fort Bragg Fever (*Worth B. Daniels, M.D.*)	437
	Recognition of a New Disease	437
	Differential Diagnosis	441
	Epidemiological Aspects	442
	Special Investigation	443
	Addendum	446
XIV	Statistics of Malaria (*Fred H. Mowrey, M.D.*)	449
	Historical Note	449
	World War II	451
	Types of Malaria	454
	Relapse in Malaria	455
	Duration of Hospitalization	459
	Deaths Due To Malaria	460
	Summary	463
XV	The Suppression of Malaria (*Benjamin M. Baker, M.D.*)	465
	Factors in Early Failures in Suppression of Malaria	466
	Effects of Atabrine Withdrawal	468
	Effect of Suppressive Therapy on Parasite Species	469
	Long-Term Clinical Experience With Atabrine Suppression	471
	Concentration of Atabrine in the Blood at Levels Effective for Suppression	473
	Undesirable Effects of Atabrine	476
XVI	Clinical Aspects of Malaria (*Harold D. Levine, M.D.*)	479
	Predisposing Factors	480
	Prodromal Symptoms	481
	Clinical Symptoms of the Acute Attack	481
	Complications of Malaria	484
	Chronic Malaria	487
	Relapses in Malaria	488
	Supporting Evidence From the Laboratory	489
	Differential Diagnosis	491
	Summary	492
XVII	Treatment of Malaria (*Perrin H. Long, M.D.*)	493
	Introduction	493
	Experience in the Pacific	495
	Experience in the India-Burma Theater	498
	Experience in the Mediterranean (formerly North African) Theater of Operations	502
XVIII	Clinical Trials of Antimalarial Drugs (*Harry Most, M.D.*)	525
	Penicillin	525
	Heavy Metals	526
	Sulfonamides	528
	Cinchona Alkaloids	531
	Quinacrine Hydrochloride (Atabrine)	538
	4-Aminoquinoline Compounds	559
	8-Aminoquinoline Compounds	579
	Summary	592
INDEX		599

Illustrations

Figure		*Page*
1	Male and female of *Phlebotomus papatasii*	54
2	Medical officers inspect water for mosquito breeding patches, Queensland, Australia	61
3	Enlisted men spray stagnant pond with kerosene guns to destroy larvae in mosquito control, Rockhampton, Australia	62
4	Conditions which favor mosquito breeding	66
5	Aerial view of Manila being sprayed against mosquitoes and flies with DDT insecticide by C–47's	68
6	Medical officer distributing mosquito repellent	71
7	Rash of dengue fever	73
8	"Ulcer" eschar in tsutsugamushi fever	115
9	Eschar on ankle in tsutsugamushi disease	141
10	Rash of tsutsugamushi disease	141
11	Maculopapular rash on third day of disease	167
12	Capillary in derma showing swelling and proliferation of endothelium to point of occlusion	173
13	Finely granular capillary thrombus, with pericapillary collection of mononuclear cells in derma	173
14	Necrosis and thrombosis of dermal capillary	174
15	Swelling and proliferation of endothelium of capillary in tongue	174
16	Occlusion of capillary in tongue by swelling and necrosis of endothelium	174
17	Myocardium	174
18	Large cerebral nodule showing its relation to a capillary	175
19	Mural thrombus in subendocardial arteriole	175
20	Granular thrombus in arteriole in submucosa of trachea and cellular infiltrate beneath basement membrane of mucosa	175
21	Cellular thrombus in arteriole of testis	175
22	Point of attachment of base of mitral valve, with disruption of elastica, edema (mucoid), infiltration of mononuclear cells, and production of fibroblasts	176
23	Acute interstitial myocarditis, with diffuse infiltration of mononuclear cells	176
24	Acute interstitial myositis of tongue, with infiltration of mononuclear cells	176
25	Small nodule of mononuclear cells in skeletal muscle attached to thyroid gland	176
26	Mononuclear infiltrate in corticomedullary junction of kidney	177
27	Focal interstitial orchitis about a dilated capillary	177
28	Mononuclear cells forming interstitial exudate in acute myocarditis	177
29	Nodules in posterior lobe of pituitary identical with those in the brain and spinal cord	178
30	Hyperplasia of sinusoidal endothelium of the liver and infiltration of mononuclear cells	178
31	Lung, alveolar exudate showing many rickettsia-like bodies in cytoplasm of polymorphonuclear leukocytes	178
32	Pancreas, infiltration of mononuclear cells in the interlobular septum, dilatation of acini, and inspissation of secretion	178
33	Counties in 11 Southern States reporting cases of endemic typhus fever, 1922–39 and 1943–45	206
34	Typhus fever patient on U.S.A. Typhus Commission Ward, Fever Hospital, Cairo, Egypt	218

Figure		*Page*
35	Rash in meningococcal bacteremia	245
36	Widespread ecchymotic rash in a patient with fulminating bacteremia and hemorrhages into the adrenals	254
37	Multiple diphtheritic ulcers of lower extremity acquired in New Zealand	285
38	Typical chronic ulcer of 4 weeks' duration	286
39	Diphtheritic skin ulcers	287
40	Penile ulcers	288
41	Epidermophytosis superinfected with *Corynebacterium diphtheriae*	289
42	Moist, desquamative, and ulcerative dermatitis	290
43	Cutaneous diphtheria as seen in the India-Burma Theater	291
44	Diphtheritic paronychiae	311
45	Toxigenic *Corynebacterium diphtheriae* in skin of palms and multiple paronychiae, acquired in the Solomon Islands	311
46	Exudate from diphtheritic ulcer	320
47	Exudate from ulcer in lesion	320
48	Chronic ulcer of ankle containing *Corynebacterium diphtheriae*	321
49	Diphtheritic ulcers in children	322
50	*Corynebacterium hemolyticum* colonies on blood agar	323
51	*Corynebacterium diphtheriae* on human blood agar	323
52	*Corynebacterium hemolyticum* on human blood agar	323
53	*Corynebacterium hemolyticum* colony as seen under low power, split lens of microscope	323
54	*Corynebacterium hemolyticum* on Löffler's serum	324
55	*Corynebacterium diphtheriae* on Löffler's serum	324
56	Poisoning by Mapharsen in treatment of syphilis	421
57	Erythematous skin lesions over the pretibial regions	439
58	Generalized form of skin eruption	441
59	Lt. Col. Garfield G. Duncan, MC, explaining malaria suppressive therapy charts to Gen. Douglas MacArthur, Queensland, Australia	467
60	Brig. Gen. James S. Simmons and Col. Arthur Fischer, GSC, inspect cinchona seedlings	531

Charts

Number		
1	Incidence of sandfly fever and fever of undetermined origin in the North African-Mediterranean Theater of Operations, U.S. Army, 1943–45	55
2	Seasonal incidence of poliomyelitis in the Army in the continental United States compared with contemporaneous civilian rates, 1943–46	92
3	Incidence of poliomyelitis in the U.S. Army, by selected area and year, 1940–48	99
4	Clinical and laboratory findings in patient with "E" severity typhus fever	148
5	Clinical and laboratory findings in a fatal case of epidemic typhus fever	150
6	Clinical course and early serological findings in a moderately severe case of epidemic typhus in a vaccinated individual	161
7	Clinical comparison of vaccinated and unvaccinated groups of typhus fever cases among employees of the Cairo Fever Hospital, El Abbasa, Egypt	165
8	Temperature chart and pertinent laboratory findings of the only known case of typhus fever occurring among U.S. Army troops in Sicily, 1943	167
9	Effect of para-aminobenzoic acid on time of death in chick embryos infected with *Rickettsia prowazeki*	196

Number		*Page*
10	Comparison of temperatures of 20 para-aminobenzoic acid treated patients and 19 alternate control patients, Cairo, Egypt, 1944 and 1945	198
11	Total reported cases of murine (fleaborne) typhus in the United States, 1931–45	207
12	Admissions to U.S. Army hospitals for meningococcal infections among troops in the continental United States, by month, World War I and World War II	240
13	Case fatality ratios for meningococcal infections, by months, in the continental United States during World War I and World War II	243
14	Number of cases of skin diseases and diphtheria and tonsillitis in the *Afrika Korps*, 1942	313
15	Diphtheria in Germany, Norway, and the Netherlands, 1939–44	317
16	Diphtheria in France, Denmark, Sweden, and Switzerland, 1939–45	318
17	Incidence of tuberculosis in the U.S. Army in the continental United States, World War I and World War II	335
18	Incidence of tuberculosis among U.S. Army troops in the United States and overseas, January 1942 to June 1946	336
19	Withdrawals from separation processing for pulmonary tuberculosis in U.S. Army separation centers, July 1945 to August 1946	337
20	Disability discharges for tuberculosis among enlisted men in the U.S. Army, 1942–45	338
21	Incidence of tuberculosis in the U.S. Army, by theater and year, 1942–45	361
22	A comparison of computed and actual rates reflecting savings attributed to improved treatment of venereal disease, Army in the United States, June 1942 to August 1945	434
23	Changes in therapy, incidence, and duration of treatment of venereal disease, Army in the United States, June 1942 to August 1945	435
24	Temperature, pulse, and leukocyte count of patient	440
25	Malaria experience of an infantry regiment carefully followed for 34 months, South Pacific Area, December 1942-August 1945	472
26	Penicillin studies in three patients with *vivax* malaria	527
27	Rate of disappearance of parasites during treatment of 497 acute attacks of *vivax* malaria with quinacrine hydrochloride or quinine	533
28	Relapse rates and intervals to relapse following treatment, by days, with quinacrine hydrochloride or quinine of 250 acute attacks of *vivax* malaria of Pacific origin	535
29	Malaria rates in an infantry regiment under various schedules of suppression with quinacrine hydrochloride, by week	547
30	Distribution of relapses in two groups of patients after treatment for acute attacks of *vivax* malaria of Pacific origin	549
31	Comparative rate of disappearance of parasites from peripheral blood during treatment of *vivax* malaria with quinine, quinacrine hydrochloride, and chloroquine	566
32	Comparative efficiency of quinine, quinacrine hydrochloride, and chloroquine in controlling fever during treatment of delayed primary attacks of relapses of *vivax* malaria	567
33	Cumulative rates of relapses during a minimum of 120 days following treatment of acute attacks of *vivax* malaria with quinine, quinacrine hydrochloride, and chloroquine	568
34	Comparison of distribution of relapses occurring during the first 60 days after treatment of acute attacks of *vivax* malaria of Pacific origin with quinine, quinacrine hydrochloride, and chloroquine	569

Number		*Page*
35	Average plasma levels of chloroquine during and after treatment under plans A, B, and C	570
36	Relapse rates and intervals to relapse after treatment of acute attacks of *vivax* malaria of Pacific origin with various drugs	584

Tables

1	Admission rates for the various designations of Vincent's infection in the U.S. Army during World War I and World War II	5
2	Admissions for primary atypical pneumonia, bacterial pneumonia, and other pneumonia, in the U.S. Army, 1942–45	27
3	Incidence of dengue in the U.S. Army, 1942–45	60
4	Incidence rates for dengue in U.S. Army personnel in New Caledonia and Espíritu Santo, from January to August, 1943 and 1944	63
5	Breeding index of *Aedes* mosquitoes in Honolulu, T.H., from August 1943 to August 1944	64
6	Incidence of dengue in U.S. Army personnel in New Guinea and adjacent islands, January 1944 to August 1945	65
7	Incidence of dengue in U.S. Army personnel in the Philippine Islands, November 1944 to December 1945	67
8	Daily report of new cases of dengue at height of the epidemic in Saipan, 14 September to 6 October 1944	70
9	Physical signs and symptoms of 418 cases of dengue in two groups in U.S. Army patients, 1944	74
10	Admissions for encephalitis in the U.S. Army, 1942–45	84
11	Deaths due to encephalitis in the U.S. Army, 1942–45	85
12	Number of cases and deaths due to scrub typhus in the Southwest Pacific Area, U.S. Army, January 1943 to August 1945	114
13	Epidemic typhus in French North Africa, Egypt, and Iran, 1930–44	145
14	Incidence of epidemic typhus fever (louseborne) in the U.S. Army, 1942–45	146
15	Serological findings and immunization record in three cases of epidemic typhus incurred subsequent to immunization with typhus fever vaccine	163
16	Clinical summary of five cases of epidemic typhus fever incurred subsequent to immunization with typhus fever vaccine	164
17	Comparison of typhus in three groups at Belsen Concentration Camp, Belsen, Germany	169
18	Weil-Felix *Proteus* agglutination tests in epidemic typhus (case 1344)	180
19	Weil-Felix *Proteus* OX-19 agglutination results on 1,002 sera from 203 patients with typhus fever	181
20	Serological findings in three typhus cases with negative Weil-Felix OX-19 agglutination results	182
21	The usual Weil-Felix reactions in rickettsial diseases	182
22	Complement fixation test results in case 1344, epidemic typhus fever	184
23	Complement fixation results on 1,002 sera from 203 patients with typhus fever	185
24	Serological findings in two cases of typhus fever with negative results in complement fixation tests	186
25	Serological findings in a patient with epidemic typhus fever contracted after receiving 5.0 cc. of Cox-type vaccine	187
26	Rickettsial agglutination test results in case 1344	189

Number		*Page*
27	Epidemic neutralizing antibody findings in case 1344	191
28	Incidence of endemic typhus fever (fleaborne) in the U.S. Army, 1942–45	207
29	Serological studies on an American soldier with murine typhus	210
30	Serological results found in individuals immunized with epidemic typhus vaccine and who subsequently contracted murine typhus	211
31	Serological findings in two cases of probable murine typhus fever occurring in vaccinated individuals at Dakar, French West Africa	213
32	Serological results in an unvaccinated individual infected with murine typhus fever (case 1)	214
33	Clinical and historical information on rheumatic fever as observed in three U.S. Army general hospitals	230
34	Incidence and deaths due to meningococcal infections, U.S. Army, World War I and World War II	242
35	Comparative mortality of certain infectious diseases in the U.S. Army, 1942–45	243
36	Cause of death in 300 cases of meningococcal infection reviewed at the Armed Forces Institute of Pathology	251
37	Severity of adrenal hemorrhage and duration of life in 126 of 300 fatal cases of meningococcal infection	256
38	Duration of life in relation to severity of illness in 118 of 144 cases of meningitis studied at the Armed Forces Institute of Pathology	257
39	Distribution of types of meningococci in 1,436 cases of meningococcal infection, Fourth Service Command Laboratory, August 1942-December 1945	261
40	Incidence of diphtheria in the U.S. Army, 1942–45	276
41	Deaths due to diphtheria in the U.S. Army, 1942–45	277
42	Incidence of cutaneous diphtheria in the U.S. Army, 1944–45	277
43	Schick reactions of individuals with diphtheritic tropical ulcers in 3 infantry divisions in the South Pacific Area	296
44	Study of influence of antitoxin on incidence of complications in diphtheria, 20th General Hospital, India-Burma Theater	305
45	Cases of diphtheria in the 27th Infantry Division in rest area in the New Hebrides, 16 September-29 October 1944	314
46	Admissions, deaths, and disability separations due to tubercular diseases in the U.S. Army (Union only), May 1861-June 1866	330
47	Incidence rates for tuberculosis in the Army in the European theater of operations and in the continental United States, 1942–45	340
48	Prevalence of tuberculosis, all forms, in U.S. Army nurses in the European theater of operations, 1942–45	343
49	Incidence of nonpulmonary tuberculosis (excludes pleural tuberculosis) in the U.S. Army, 1942–45	369
50	Incidence of tuberculosis of pleura and serofibrinous pleuritis in the U.S. Army, 1944–45	371
51	Admissions and readmissions for spontaneous pneumothorax in the U.S. Army, 1942–45	373
52	Deaths due to tuberculosis in the U.S. Army, 1942–45	377
53	Total attack rate for malaria in the U.S. Army, by type of plasmodium, 1942–45	454
54	Attack rates of malaria, all forms, in the U.S. Army, 1942–45	455
55	Attack rates of vivax (tertian) malaria, in the U.S. Army, 1942–45	456
56	Attack rates of falciparum (estivo-autumnal) malaria, in the U.S. Army, 1942–45	456
57	Attack rates of malariae (quartan) malaria, in the U.S. Army, 1942–45	457

Number		*Page*
58	Attack rates of mixed malarial infections, in the U.S. Army, 1942–45	457
59	Attack rates of other and unspecified forms of malaria, in the U.S. Army, 1942–45	458
60	Average number of days in hospital and quarters for admissions and readmissions due to malaria and fever of undetermined origin, in the U.S. Army, 1942, 1943, and 1945	460
61	Deaths due to malaria, in the U.S. Army, 1942–45	460
62	Deaths due to vivax (tertian) malaria, in the U.S. Army, 1942–45	461
63	Deaths due to falciparum (estivo-autumnal) malaria, in the U.S. Army, 1942–45	461
64	Deaths due to malaria, mixed type, in the U.S. Army, 1942–45	462
65	Deaths due to malaria, unclassified and other, in the U.S. Army, 1942–45	462
66	Malaria cases in the Mediterranean (formerly North African) Theater of Operations, U.S. Army, 1942–45	503
67	Experience of 32 hospitals with malaria during the entire period of operation in the Mediterranean (formerly North African) Theater of Operations, U.S. Army, to August 1944	504
68	Malaria cases discharged from all hospitals in the Mediterranean (formerly North African) Theater of Operations, U.S. Army, 15 September 1944 to 11 May 1945	505
69	Results of study of duration of fever after start of treatment in 28 quinine-treated cases and 24 Atabrine-treated cases of malaria	511
70	Incidence of attacks of malaria reported by 27 hospitals in the Mediterranean (formerly North African) Theater of Operations, U.S. Army	515
71	Incidence of relapses due to malaria reported by 18 hospitals in the Mediterranean (formerly North African) Theater of Operations, U.S. Army	515
72	Malaria patients evacuated to the Zone of Interior from the Mediterranean (formerly North African) Theater of Operations, U.S. Army, 25 hospitals reporting	516
73	Experimental field tests with sulfamerazine, Atabrine, and sulfapyrazine	530
74	Representative treatment schedules for chloroquine	565
75	Relative efficiency of quinine, quinacrine hydrochloride, and chloroquine in treatment of acute attacks of *vivax* malaria	569
76	Results of treatment in four groups of patients administered antimalarial drugs for acute attacks of *vivax* malaria of Pacific origin	584

CHAPTER I

Respiratory Diseases

Yale Kneeland, Jr., M.D.

GENERAL CONSIDERATIONS

Diseases of the respiratory tract may be divided into two groups: The acute infections and the chronic diseases which may or may not be infectious. Most of these conditions will be dealt with in this chapter, although certain exceptions will be made. For example, in World War II, the interrelationship of tonsillitis, scarlet fever, rheumatic disease, and nephritis was intensively studied; the subject of streptococcal infections as a whole will be discussed elsewhere. Similarly, two chronic infections, tuberculosis and coccidioidomycosis, will be described by others. Lastly, chronic sinusitis, aerootitis, and the like, are primarily the concern of the otologist and will not be considered here.

The acute respiratory diseases which immediately come to mind are the common cold, influenza, and pneumonia. These are communicated by droplets and droplet nuclei and are thus allied to certain virus infections, such as measles, which are also presumably transmitted in this way. Certain communicable diseases of childhood will also be included here. Cerebrospinal fever and diphtheria, however, although their portal of entry is the respiratory tract, will be discussed elsewhere in this volume. Clinical syndromes of unknown etiology, bizarre manifestations occurring only in localized outbreaks and not generally recognized as disease entities, are not included. This still leaves a large field for discussion.

Any general consideration of disease in World War II immediately invites comparison with the experience in World War I. Exact comparisons of morbidity and mortality of acute respiratory diseases in the two wars are not, however, possible for two reasons: First, more exact knowledge of the diseases led to a change in terminology; and second, certain new concepts, for example, that of atypical pneumonia, evolved. In spite of this, a rough and startling comparison may be made of the 46,640 deaths from influenza, lobar pneumonia, bronchopneumonia, bronchitis, and measles in the First World War,[1] roughly 73 percent of total deaths from disease, and the 1,285 deaths from the same causes in the Second World War when an army well over twice the size of that of World War I was mobilized for a longer period.

Factors which played a role in this extraordinary change in importance of the disease just mentioned were the advent of sulfonamides and anti-

[1] The Medical Department of the United States Army in the World War. Washington: U.S. Government Printing Office, 1928, vol. IX.

biotics, the absence of pandemic influenza of the 1918 type, an apparent change in the whole pattern of respiratory infection between the wars, and a greater degree of immunity to certain communicable diseases in the general population. The last was probably brought about by greatly increased communications which lessened isolation of rural areas. In addition, the almost universal roentgen examination of the chest at induction undoubtedly lowered the incidence of chronic pulmonary diseases found in troops during World War II.

In the following pages, the occurrence and course of each disease in question during World War II is discussed, with emphasis placed upon problems of diagnosis, treatment, and general management which were significant in a military sense. The chief military significance of many of the acute communicable diseases is epidemiological, and this aspect of the question has been exhaustively presented in other volumes in the history of the Medical Department in World War II.[2] It is obvious that in many instances information will overlap. Some of the material will of necessity be repetitious.

Insofar as possible, proper names are avoided in the text, but where published material has been drawn upon, full acknowledgment is given. Other sources employed are as follows: Preliminary data from the Medical Statistics Division, Office of the Surgeon General; the writer's own notes while he served as consultant in an oversea theater; essential technical medical data sent in by various theater surgeons; reports submitted by medical consultants throughout the world; and other unpublished notes, manuscripts, and memorandums in the Professional Service Division, Office of the Surgeon General.

Part I. Acute Respiratory Diseases

COMMON UPPER RESPIRATORY INFECTION

Introduction

The term "common upper respiratory infection" includes a heterogeneous group of ill-defined conditions. In fact, it is a kind of scrapbasket which encompasses all the acute respiratory diseases after eliminating the pneumonias and influenza. In a general way, the group includes the common cold; nasopharyngitis which may or may not be due to the influenza virus; infection of the pharynx and tonsils produced by certain micro-organisms, such as the hemolytic streptococcus and Vincent's organisms; and bronchi-

[2] (1) Medical Department, United States Army. Preventive Medicine in World War II. Volume IV. Communicable Diseases Transmitted Chiefly Through Respiratory and Alimentary Tracts. Washington: U.S. Government Printing Office. 1958. (2) Medical Department, United States Army. Preventive Medicine in World War II. Volume V. Communicable Diseases Transmitted Through Contact or By Unknown Means. Washington: U.S. Government Printing Office. 1960. (3) Medical Department, United States Army. Preventive Medicine in World War II. Volume VI. Communicable Diseases: Malaria. [In press.] (4) Medical Department, United States Army. Preventive Medicine in World War II. Volume VII. Communicable Diseases: Arthropodborne Diseases Other Than Malaria. [In preparation.]

tis. The latter is a loose term limited by some physicians to cases in which dry rales are audible; that is, the asthmatic type, while others may use it to describe an acute respiratory infection with substernal soreness and paroxysmal cough. It is probable that the viruses of common respiratory diseases, influenza, and atypical pneumonia can all produce this clinical picture, and it may also be the result of infection by such organisms as pneumococci or *Hemophilus influenzae* following a cold. In any cases, it is not an etiological entity

The common cold had been shown before World War II to be primarily a virus disease.[3] Experimental studies are handicapped by the fact that only man and the anthropoid ape are susceptible to the virus, and such questions as that of immunity and whether the virus is an entity or whether several distinct viruses exist were not settled. The Commission on Acute Respiratory Diseases of the Army Epidemiological Board (Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army) during the war undertook, under the direction of Dr. John H. Dingle, to investigate the transmission of common respiratory diseases. Evidence was produced[4] that there are at least two viruses: One, the coryzal type with a short incubation period, producing little if any active immunity; the other, with a longer incubation period, giving rise to more constitutional symptoms, often attended by fever, and conferring immunity against homologous reinoculation. The second type came to be known as "undifferentiated respiratory disease." As the number of transmission experiments was small, there is no information as to the relative frequency of infection with these two agents. Recent observations by Atlas[5] suggest that more viruses of common respiratory infection may exist.

The presence of pathogenic bacteria in the upper respiratory tract adds to the complexity of the etiology of common respiratory diseases. Purulent complications, such as otitis and sinusitis, are due to bacterial infection, but there is no proof of the role played by identified pathogenic organisms in the production of subacute catarrhs, sphenoethmoiditis, and the like. The best opinion during the war, confirmed by the use of chemotherapeutic agents in adults,[6] was that the average cold is a fairly pure virus disease, but that the relationship of virus to bacteria was often not clear.

Colds are, on the whole, more serious in infants than in adults. Infants usually develop a fever with a cold, and complications are more frequent.

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[3] Doches, A. R., Mills, K. C., and Kneeland, Y., Jr.: Studies on the Common Cold: Cultivation of Virus in Tissue Medium. J. Exper. Med. 63: 559-579, April 1936.

[4] Commission on Acute Respiratory Diseases: Experimental Transmission of Minor Respiratory Illness to Human Volunteers by Filter-Passing Agents. I. Demonstration of Two Types of Illness Characterized by Long and Short Incubation Periods and Different Clinical Features. II. Immunity in Reinoculation With Agents From the Two Types of Minor Respiratory Illness and From Primary Atypical Pneumonia. J. Clin. Investigation 26: 957-973; 974-982. September 1947.

[5] Atlas, L. T.: Minor Respiratory Diseases; Studies With Four Agents in Human Volunteers. Abstract in J. Clin. Investigation 32: 552-553, June 1953.

[6] Cecil, R. L., Plummer, N., and Smillie, W. G.: Sulfadiazine in the Treatment of the Common Cold. J.A.M.A. 124: 8-14, 1 Jan. 1944.

Various pathogenic bacteria are more conspicuous in cultures made from children,[7] and this suggests that they may have some influence on the severity of colds even in the absence of definite purulent complications. Controlled studies made during the early war years of the use of sulfonamides in very highly susceptible children support this concept.[8]

It was the writer's impression that soldiers reacted to common respiratory diseases in a manner more suggestive of childhood than of adult life. They tended to develop fever of higher degree than that seen in general civilian life. Youth, exposure, and crowding probably contributed to this clinical pattern. Incidence of infection with the virus of undifferentiated respiratory disease may have been higher in the Army than in civilian life. Whatever the reasons, the acute phase of the common cold was apt to be more prostrating to soldiers than to office-working civilians. However, the soldier's convalescence was usually rapid.

Severe throat infections caused by the hemolytic streptococcus, scarlet fever, and rheumatic fever will be discussed elsewhere. However, a certain proportion of admissions to the respiratory service of an Army hospital were infections caused by this organism. Various complications to the usual sore throat or inflammation of the lymphatic tissue are recognized, but in the Army the most common was peritonsillar cellulitis.

The clinical picture of exudative pharyngitis is well recognized, and when an acute tonsillitis or pharyngitis is observed showing whitish exudate, most physicians assume it is caused by hemolytic streptococci. However, when endemic exudative pharyngitis was studied closely by the Commission on Acute Respiratory Diseases,[9] in only about 50 percent of cases could the hemolytic streptococcus be recoverd on culture and in only half of these was there a rise in the titer of streptococcal antibody during convalescence to suggest that the organism was playing an important role in the disease. Since in only 25 percent of the cases of endemic exudative disease was the laboratory evidence for streptococcal infection complete, the Commission designated the other cases as nonstreptococcal exudative pharyngitis, and some speculation occurred as to the possible viral origin of this condition. Although, in the aggregate, cases of proved hemolytic streptococcal pharyngitis differ clinically from the nonstreptococcal variety, mild cases may be indistinguishable.

Vincent's organisms may also at times produce throat lesions which resemble streptococcal infections. The appearance of a typical case of so-called Vincent's organisms differed, however, from that of a streptococcal infection. The thick pseudomembrane and the tendency to ulceration were

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[7] Kneeland, Y., Jr., and Dawes, C. F.: Studies on the Common Cold; The Relationship of Pathogenic Bacteria to Upper Respiratory Disease in Infants. J. Exper. Med. 55: 735-744, May 1932.

[8] Siegel, M.: Studies on Control of Acute Infections of the Respiratory Tract. II. Oral Administration of Sulfadiazine at the Onset of Acute Respiratory Illness. Am. J. Dis. Child. 66: 114-120, August 1943.

[9] Commission on Acute Respiratory Diseases: Endemic Exudative Pharyngitis and Tonsillitis; Etiology and Clinical Characteristics. J.A.M.A. 125: 1163-1169, 26 Aug. 1944.

characteristic, but differential diagnosis was not always possible, and it was always necessary to rule out diphtheria. Vincent's stomatitis presented itself often as only a dental problem, but occasionally the throat was involved as well as the gums; likewise, Vincent's infection of the throat without involvement of the gums was also encountered. A comparison of the admission rates for the various designations of Vincent's infection in World Wars I and II is presented in table 1.

TABLE 1.—*Admission rates for the various designations of Vincent's infection in the U.S. Army during World War I and World War II*

[Rate expressed as number of cases per annum per 1,000 average strength]

Diagnostic terminology	Admission rate			
	World War I	World War II		
		1942–45	1942–43	1944–45
Trench mouth	0.02	0	1.94	0
Vincent's angina	[1] 1.56	0	0	0
Vincent's infection (not elsewhere classified)	0	0	2.30	0
Vincent's infection (all forms)	[1] 1.58	3.93	4.24	3.73

[1] Enlisted personnel only.

Experience in the Continental United States

Noneffectiveness

Common upper respiratory infection was the most prolific cause of noneffectiveness in the U.S. Army. A graphic representation of its incidence in the Army from 1925 to 1945, inclusive, would show a sharp rise around the beginning of each year. An unusual peak was reached around the beginning of 1941, when no major general epidemic was prevalent. This military peak was coincident with a rapid increase in mobilization, the opening of new camps, and the hurried assembly of large numbers of unseasoned civilians.

A careful statistical analysis presented by Dr. Philip E. Sartwell in another volume in the history of the Medical Department in World War II shows that the magnitude of incidence of common respiratory diseases in any area is related to the proportion of new recruits.[10] It is conceivable that the unexpected increment of respiratory infection in recruits was due to infection with the virus of undifferentiated respiratory disease; that is, the one which leaves some active immunity in its wake. The seasoning of troops is of military importance insofar as common respiratory diseases are concerned as it governs the amount of noneffectiveness to be expected.

For the remainder of the war, the curve of incidence of common respiratory diseases in the United States was astonishingly symmetrical. At about

[10] See footnote 2 (1), p. 2.

the same time during each war year, there was a recurring peak of almost the same dimension. Individual differences in type of disease and frequency at various stations were cancelled out by the large numbers and wide geographic distribution.

Streptococcal infections were particularly numerous in the eastern slopes of the Rocky Mountains and the Great Lakes area. Here, they were the subject of considerable study both in their less conspicuous form as part of the mosaic of common respiratory disease and when they became epidemic and were associated with scarlet fever and rheumatic fever. In cases associated with common respiratory disease, treatment varied in different stations. The types and amount of sulfonamides employed differed, although, when available, sulfadiazine was probably the most widely used. Controlled studies [11] in large numbers of cases indicated that sulfadiazine had no more effect than the routine APC capsule on the duration of the febrile period or on the length of hospital stay. In more severe cases, however, the drug seemed to limit spread, to lessen cervical lymphadenitis, and to prevent the development of frank abscess.

A study of air disinfection directed by the Army Epidemiological Board demonstrated that certain glycols, when vaporized, killed micro-organisms [12] and also influenza virus.[13] These substances seemed wholly nontoxic in bactericidal concentration, but their efficacy was influenced by environmental factors, such as humidity.[14] Under clinical conditions, they diminished airborne cross-infection.[15] These reports represented progress in the control of infection, but practical limitations in the application of aerosols prevented their use in the field. Oiling floors and bedding, another method aimed at reduction of airborne infection, could not be shown to lower incidence of common respiratory infection at Fort Bragg, N.C.

In summary, common upper respiratory infection, while the commonest single cause of military noneffectiveness, did not seriously interfere with the training program. Prolonged disability as a sequel was almost entirely limited to the streptococcal infections. Mortality was insignificant.

Experience Overseas

Incidence.—The "transport cold" was a well-known feature of crossing the Atlantic in wartime. Its widespread occurrence could be attributed to

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[11] Rusk, H. A., and van Ravenswaay, A. C.: Sulfadiazine in Respiratory Tract Infections; Its Value in Treatment During the Winter of 1942–1943 at Jefferson Barracks, Missouri. J.A.M.A. 122: 495–496, 10 June 1943.

[12] Robertson, O. H., Bigg, E., Miller, B. F., and Baker, Z.: Sterilization of Air by Certain Glycols Employed as Aerosols. Science 93: 213–214, 28 Feb. 1941.

[13] Robertson, O. H., Bigg, E., Puck, T. T., and Miller, B. F.: Protection of Mice Against Infection With Air-Borne Influenza Virus by Means of Propylene Glycol Vapor. Science 94: 612–613, 26 Dec. 1941.

[14] Robertson, O. H.: Sterilization of Air With Glycol Vapors. Harvey Lect. (1942–1943) 38: 227–254, 1943.

[15] Harris, T. N., and Stokes, J., Jr.: Air-Borne Cross-Infection in the Case of the Common Cold. A Further Clinical Study of the Use of Glycol Vapors for Air Sterilization. Am. J.M. Sc. 206: 631–636, November 1943.

the great crowding, poor ventilation, and the bringing together of troops from many different units, thus introducing new infective strains. It was commonplace for as high as 80 percent of U.S. troops to contract a cold in the course of the voyage to England.

In spite of the climate in England, colder and damper than that to which Americans had been accustomed, the noneffective rate due to respiratory diseases was considerably lower there than in the United States. The fact that U.S. troops were seasoned when they arrived undoubtedly contributed to the lower rate. In some Americans, the cold had a tendency to become chronic, particularly during the first year overseas, but usually thereafter the men had become acclimatized, and chronic catarrh and cough were much less marked. Individuals with a history of recurrent bronchitis were apt to have difficulty with the English climate; in particular, any tendency to asthma seemed accentuated. On the whole, however, the health of the Army was excellent, and there was no undue incidence of sinusitis.

The incidence of common upper respiratory disease and influenza in the European Theater of Operations, U.S. Army, pointed up the result of seasoning of troops. In November 1943, at the time of the epidemic of influenza A, the incidence was slightly higher than in January 1943 when influenza was not identified. After November 1943, there was a steady decline so that in June 1944 and thereafter throughout the winter of 1945 the noneffective rate was at a very low level.

Clinical features of common upper respiratory infection in the European theater were not remarkable. Throat cultures yielded moderate numbers of higher type pneumococci and *H. influenzae.* The number of hemolytic streptococcus carriers was not large, and only sporadic cases of streptococcal sore throat appeared during the winter months. The tendency to develop peritonsillar cellulitis has been mentioned. In 80 percent of such cases, the hemolytic streptococcus could be cultivated. The remaining 20 percent, clinically indistinguishable, may represent cases of nonstreptococcal exudative pharyngitis with an unusual degree of swelling of faucial pillars.

The incidence of common respiratory infection in the Mediterranean (formerly North African) Theater of Operations, U.S. Army, was considerably below the average for the European theater and for the United States in 1942 and 1943. In the summer of 1944, it was slightly higher, but at this time morbidity elsewhere was unusually low. Common respiratory disease presented one special problem in the Mediterranean theater—the likelihood of its being confused with certain conditions which were endemic in the area, particularly sandfly fever, malaria, and the preicteric stage of hepatitis. Complications of common respiratory infections were not conspicuous, and a total of but 10 deaths was recorded from such purulent infections as meningitis.

Incidence of streptococcal infections in the Mediterranean theater was low. According to Circular Letter No. 16, Headquarters, North African

Theater of Operations, Office of the Surgeon, 22 March 1944, subject: Preparation of Medical Department Reports and Records, U.S. Army, the term "streptococcal sore throat" was applied only to acute pharyngitis and tonsillitis known or suspected to be caused by the beta hemolytic streptococcus, and foodborne and milkborne outbreaks of septic sore throat. During the 11-month period from 1 May 1944 to 31 March 1945, inclusive, when streptococcal sore throat was reported separately, only 803 cases were reported. Two small outbreaks were studied, one involving 112 men and the other, 38. In both instances, it was thought that the streptococcal infection was either foodborne or milkborne. Interestingly enough, not a single case of scarlet fever developed as a result of these outbreaks.[16]

An acute outbreak of membranous pharyngitis in Sicily, in October 1943, involved 96 men, 66 of whom were reported by the local civilian laboratories as having throat cultures positive for *Corynebacterium diphtheriae*. Subsequent investigation by the staff of the 15th Medical General Laboratory, Naples, Italy, threw doubt on the diagnosis of diphtheria in this outbreak, and the theater consultant in medicine later expressed the opinion that in all probability it was of streptococcic origin. The epidemic was explosive and had the character of a foodborne or milkborne infection.

Vincent's angina (as distinct from stomatitis or trench mouth) was reported only 990 times from the Mediterranean theater. Nevertheless, the estimated admissions for the various types of Vincent's infection numbered about 2,800.

The admission rate for common respiratory infection in U.S. Army Forces, China-Burma-India, was comparable with that observed in temperate climates, although the curve of incidence was relatively devoid of seasonal peaks. Clinical characteristics were stated to be astonishingly similar to those noted in the United States, and the complications as frequent.

The Pacific area is so vast that generalizations about disease therein would be dangerous. Conditions in parts of Australia are quite similar to those in temperate regions elsewhere, and common upper respiratory infection conformed to the familiar pattern. On small tropical islands, however, the incidence was stated to be much less under normal conditions, rising sharply with the arrival of large numbers of troops. Studies have been reported from such areas indicating that the bacterial flora was different from that noted in temperate climates. One study,[17] for instance, included 272 throat and sputum cultures in which pneumococci were found only 7 times. It was stated in this report that pneumonia was very infrequent.

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[16] Report [Final], Lt. Col. Daniel W. Myers, MC, and Maj. Edward deS. Matthews, MC, MTOUSA, to Office of the Surgeon General, subject: Respiratory Diseases in the Mediterranean Theater of Operations, 1945.

[17] Norris, R. F.: Symposium on Recent Advances in Medicine: Observations on the Epidemiology and Bacteriology of Acute Respiratory Tract Infections Among the Armed Forces of the Tropical South Pacific. M. Clin. North America 28: 1418-1427, November 1944.

Two U.S. Navy observers[18] stated that at least 50 percent of the cases of catarrhal fever in a South Pacific Area showed asthmalike manifestations. An eosinophilia of 8 to 10 percent was a common finding. The significance is obscure unless it is related to the high incidence of allergic disorders in the Tropics.[19]

Treatment.—Treatment of common upper respiratory infections was symptomatic and lacked uniformity. Apart from streptococcal and Vincent's infections, this group is not susceptible to chemotherapy. Nevertheless, it is unquestionable that a great many viral infections were treated with sulfadiazine. The greater the experience of the medical officer, and the better his facilities for laboratory diagnosis, the less unnecessary sulfonamides were administered. The Professional Service Division advised that sulfonamides should not be employed as a routine measure in the absence of definite indications. In doubtful cases, however, it seemed wise to prescribe them. If certain indications were present, such as leukocytosis, symptoms of otitis media, the presence of pneumococci in the sputum, or the clinical features of acute tonsillitis, sulfonamides, and particularly sulfadiazine, were employed.

Sulfadiazine was used in the treatment of recognized streptococcal infections with prompt effect. It was likewise employed in Vincent's infection.

In the winter of 1945, studies were made, in a number of hospitals in England, of the effect of local penicillin therapy, either in the form of a throat spray or more frequently of lozenges containing 500 units of penicillin. Results in streptococcal infections were disappointing. The use of intramuscular penicillin was also reported in a few hospitals. Its effects in streptococcal infection were said to resemble those with sulfadiazine. Local and intramuscular penicillin gave striking results in Vincent's infections in reports from England, but variable results were obtained in a small number of cases of Vincent's angina when penicillin was used intramuscularly in the Mediterranean theater.

INFLUENZA

Introduction

The word "influenza" has been in general English usage since the 16th century to designate irregularly recurring, widespread visitations of respiratory diseases, explosive in character and often associated with considerable mortality. Its recognition, until the introduction of the new serological methods, rested upon epidemiological and not clinical grounds, and one could not speak of an isolated case.

Good clinical descriptions of these outbreaks are available. Worldwide attention was directed to the disease in 1889 because of its high incidence

[18] Schneierson, S. J., and Wilson, W. A.: Unusual Feature of Respiratory Infections in a South Pacific Area. U.S. Nav. M. Bull. 44: 1010-1012, May 1945.

[19] Young, C. T., Cook, W. R., and Kawasaki, I. A.: Allergic Rhinitis and Asthma in Hawaii. War Med. 3: 282-290, March 1943.

and the relatively frequent association with fatal pneumonia during that epidemic. The influenza bacillus, isolated by Pfeiffer from a number of those fatal cases, was regarded for some years as the cause of the disease. Pandemic influenza revisited the world in a more devastating form in 1918, toward the end of the First World War. Incidence was very high, distribution global, and the mortality appalling. In the U.S. Army alone, 24,664 deaths were attributed to the disease, and the number of deaths throughout the world ran into millions.[30] This catastrophe gave rise to a most intensive scientific investigation of the disease which revealed that the Pfeiffer bacillus could not be found in many typical cases of influenzal pneumonia. These pneumonias usually had a mixed bacterial flora, among which pneumococci and streptococci were prominent. The conclusion became inescapable that some wholly different agent, not recognizable by ordinary bacteriologic means, was the primary cause of the pandemic; that this agent, while occasionally killing in a few hours, usually produced its lethal effect by paving the way for a secondary bacterial pneumonia; and that the agent was often, though not always, accompanied by Pfeiffer's bacillus. If this agent were not bacterial, it must be in the category of the filterable viruses.

The highest mortality of the 1918 pandemic was in the age group between 20 and 35 years. Susceptibility to the most severe form of the disease seemed to increase with age until about 35 years, when it fell off sharply. This suggests that exposure to the primary agent in 1889 may have increased resistance in 1918 and that the two pandemics were caused by the same virus.

Before and after the influenza outbreak of 1918, epidemic waves of acute respiratory diseases occurred which were clinically indistinguishable from mild cases in the pandemic. However, in these outbreaks, cases were uncomplicated and mortality was nil. These epidemics were called influenza of the interpandemic type or simply epidemic influenza.

Intensive study of epidemic influenza during the past 15 years was begun in England where the first successful isolation of a virus capable of infecting laboratory animals was achieved. Investigators throughout the world have contributed to the work, the principal ones being Andrewes in England, Francis in the United States, Burnet in Australia, and Smorodintsev in Russia. From these researches, a fairly clear pattern has emerged although there remain distinct gaps in our understanding of the disease.

Two causative agents have been identified. Influenza A virus, the first to be recognized, gives rise to epidemics which, in the Northern Hemisphere, tend to occur biennially in odd-numbered years in the winter months, with larger outbreaks every fourth year. Recent studies have shown that influenza A is a group of which the various agents are related but immunologically distinguishable.

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[30] The Medical Department of the United States Army in the World War. Washington: Government Printing Office, 1925, vol. XV, pt. 2, p. 134.

Influenza B virus has appeared less regularly and less explosively and has caused less severe epidemics. It was first identified in the United States in 1940, and retrospective study of sera saved from the 1936 epidemic of influenza found them to contain antibodies to this virus. Clinically, it cannot be distinguished from the disease caused by influenza A. Identification may be by isolation of the virus or by demonstrating a rise in titer of antibody to one of the two viruses following an attack. However, in some cases of influenza, identification of neither virus can be made. On the other hand, during an epidemic of one type, a significant proportion of sera may later show evidence of infection by the other type.[21]

Exceptions to the general statement that epidemic influenza tends to be mild must be noted. For example, in Boston, Mass., in December 1940 and January 1941, 66 cases of staphylococcal pneumonia with 21 deaths occurred with coincident infection with influenza A in many of these.[22] The Commission on Acute Respiratory Diseases recorded an outbreak of type I pneumococcal infection in Northville, N.Y., related to influenza B infection.[23] In a station such as the Army Air Force Technical School at Sioux Falls, S. Dak., the already constant, rather high incidence of lobar pneumonia rose when influenza appeared.

Active immunity acquired during an attack of influenza appears from clinical and serological evidence to be of short duration. Complete correlation between the level of serological immunity and susceptibility to the disease is not possible although the Commission found some evidence that patients with initially low antibody titer tended to be more severely ill than those with an initially high titer. Reference will be made later to the first large-scale attempt at active immunization of Army personnel with artificially cultivated influenza vaccine.[24]

What light do these studies of influenza throw upon the pandemic of 1918? Slight epidemiological evidence that the pandemics of 1889 and 1918 were caused by the same agent and that therefore the interpandemic variety is immunologically distinct has been mentioned. On the other hand, Shope's work on swine influenza, a persistent disease which first appeared in 1918, has suggested another hypothesis. The virus of swine influenza is related to, but not identical with, influenza A virus. If it is in reality a survival in another species of the 1918 human influenza, then one may suppose that pandemic and interpandemic influenza are related. These questions may be answered if another pandemic appears. Had such an event transpired during World War II, it would likely not have created the disaster of 1918

[21] Lush, D., Stuart-Harris, C. H., and Andrewes, C. H.: The Occurrence of Influenza B in Southern England. Brit. J. Exper. Path. 22: 302-304, December 1941.

[22] Finland, M., Peterson, O. L., and Strauss, E.: Staphylococcic Pneumonia Occurring During an Epidemic of Influenza. Arch. Int. Med. 70: 183-205, August 1942.

[23] Commission on Acute Respiratory Diseases and the New York State Department of Health: The Relation Between Epidemics of Acute Bacterial Pneumonia and Influenza. Science 102: 561-563, 30 Nov. 1945.

[24] See footnote 19, p. 9.

because complications and therefore mortality might have been very favorably affected by chemotherapy and antibiotic treatment.

For a complete account of the epidemiology of influenza during World War II, the reader is referred to the chapter by Dr. Thomas Francis, Jr., in another volume in the history of the Medical Department in World War II.[25] In the ensuing paragraphs, only the highlights most relevant to the interests of the Professional Service Division will be presented.

Experience in the Continental United States

Influenza was epidemic in the winter of 1940–41, but the major epidemic took place at the end of 1943. It was explosive in character, but not all parts of the country were simultaneously affected. It is of interest that evidence of infection with influenza A virus was found in three patients in May in a station hospital in Michigan, and on 18 November, at the very beginning of the epidemic, the same virus was recovered from two patients also in Michigan.[26] Thereafter, during the epidemic, influenza A appeared in various parts of the country. As in other epidemics, in a number of clinically typical cases, no rise in antibody titer to influenza A virus could be demonstrated, and there were rare cases in which influenza B virus appeared to be involved.

The epidemic was fairly widespread, both in the Army and among civilians, but like other outbreaks of the interpandemic type, the disease was of very short duration, rather mild in character, and generally uncomplicated. Extensive clinical and serological studies were made by the Commission at Fort Bragg.[27] Some of the conclusions drawn are as follows: Influenza with typical features—sudden onset, severe malaise, painful eyeballs, flushed face, injected eyes, high fever, and leukopenia—occurred as a clinical entity in only about half the serologically proved cases. Moreover, certain cases of undifferentiated respiratory disease, prevalent at the time, presented the same characteristics. In the aggregate, there were significant differences between undifferentiated respiratory disease and influenza, but individual cases could not be distinguished clinically.

In some areas, the 1943 influenza epidemic assumed a slightly more severe character. An example of this occurred at the Army Air Force Technical School in Sioux Falls where the first definite case was noted on 22 November. Following this, the incidence rose very sharply, the peak being reached between 29 November and 1 December. Respiratory disease admissions per 1,000 per week for the 4 weeks beginning 14 November through the week beginning 5 December were: 7.8, 13.7, 99.0, and 19.6, respectively. Altogether, 11.1 percent of the school population was affected. Age, length

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[25] See footnote 2 (1), p. 2.

[26] Salk, J. E., Menke, W. J., and Francis, T., Jr.: Identification of Influenza Type A in the Current Outbreak of Respiratory Disease. J.A.M.A. 124: 93, 8 Jan. 1944.

[27] Commission on Acute Respiratory Diseases: Studies of the 1943 Epidemic of Influenza A. II. Comparison of the Clinical and Laboratory Characteristics of Influenza A and Undifferentiated Acute Respiratory Disease (ARD). Am. J. Hyg. 48: 263-275, November 1948.

of service, and duration of stay at the post had no detectable effect upon susceptibility. Clinically, the cases were typical of influenza; throat cultures on 137 patients showed hemolytic streptococci in 17 and pneumococci in 7. There was no evidence that the epidemic engendered the spread of beta hemolytic streptococci.

Associated pneumonitis was said to be present in 5.8 percent of the patients. In these cases, onset and symptoms were similar to the uncomplicated ones, but the disease was more severe, the fever higher and of slightly longer duration (3.2 days average), and there were rales at the bases together with X-ray changes. There was no associated leukocytosis, and sulfonamides did not shorten the duration of fever. Influenzal pneumonia—which this picture most assuredly suggests—has been very uncommonly found elsewhere. In addition, at Sioux Falls, there was a sharp rise (from 1.5 to nearly 5 per 1,000) in the weekly incidence of lobar pneumonia, the peak corresponding precisely with that of influenza.

By 1943, the production of a vaccine made with artificially cultivated influenza virus had been greatly improved, and a quantity of material containing both the A and B viruses was available for testing during the epidemic. Vaccination of man with both the A and B viruses had been shown not only to stimulate the production of antibodies but also to induce considerable immunity against the artificially induced disease.[28] The active immunity to type A was apparently of shorter duration than to type B, as those vaccinated with the former 4 months before the test were considerably more susceptible than those vaccinated 2 weeks before. A large-scale trial seemed warranted. By great good fortune, some 6,263 students in the Army Specialized Training Program were vaccinated just before the epidemic. The subsequent incidence of influenza was significantly less than that in 6,211 controls, the ratio being 1:3.2.[29]

Evidence of influenza B infection was established in local outbreaks in different parts of the continental United States, in the Canal Zone, Alaska, and Hawaii in the spring of 1945. The occurrence of some influenza in the spring was reminiscent of the year 1918, and this led the chairman of the Army Epidemiological Board to recommend that the entire Army be vaccinated. The proposal was approved by The Surgeon General, U.S. Army, and was carried out in October 1945. From this uncontrolled experiment, two conclusions[30] could be drawn by comparing disease rates in the Army with those of unvaccinated U.S. Navy personnel. The first was that mass

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[28] (1) Francis, T., Jr., Salk, J. E., Pearson, H. E., and Brown, P. N.: Protective Effect of Vaccination Against Induced Influenza A. Proc. Soc. Exper. Biol. & Med. 55: 104-105, February 1944. (2) Salk, J. E., Pearson, H. E., Brown, P. N., and Francis, T., Jr.: Protective Effect of Vaccination Against Induced Influenza B. Proc. Soc. Exper. Biol. & Med. 55: 106-107, February 1944.

[29] Commission on Influenza: A Clinical Evaluation of Vaccination Against Influenza; Preliminary Report. J.A.M.A. 124: 982-985, 1 Apr. 1944.

[30] (1) Francis, T., Jr., Salk, J. E., and Brace, W. M.: The Protective Effect of Vaccination Against Epidemic Influenza B. J.A.M.A. 131: 275-278, 25 May 1946. (2) Hirst, G. K., Viches, A., Rogers, O., and Robbins, C. L.: The Effect of Vaccination on the Incidence of Influenza B. Am. J. Hyg. 45: 96-101, January 1947.

vaccination had exerted a definitely protective effect in lowering mortality, and the second, that influenza B was a better immunizing agent than influenza A.

Experience Overseas

European theater

The history of influenza in the U.S. Army in the European theater is extraordinarily interesting in the light of what might have happened. Since 1931, epidemics had occurred in England in the odd-numbered years with a larger wave every fourth year. Had this schedule been maintained, a moderate outbreak would have occurred in January 1943 and a more severe one in January 1945. The former would not have been serious as hospital facilities in England were more than adequate to care for all troops then stationed there. However, in 1945, hospitals were already filled beyond normal capacity. A sharp epidemic at that time would have been extremely difficult to cope with and its effect upon the military situation would have been grave. It is not known why the epidemic did not occur.

There is seldom a complete explanation of any epidemiological phenomenon. In this instance, the events were as follows: The January 1943 epidemic did not take place; it was delayed 10 months, until November, when a sharp, widespread epidemic developed. The rhythmic pattern of influenza was thus disturbed. Late in 1944, the senior consultant in infectious diseases, European theater, ventured to predict to the surgeon, United Kingdom Base, that influenza would not occur in 1945. Partly as a result of this point of view, many hospitalized patients with trenchfoot were retained for duty in the theater rather than being boarded home in order to increase the number of available hospital beds. It required some fortitude to make the prediction of a healthy winter from the respiratory standpoint, but, mirabile dictu, precisely this came to pass, and the U.S. Army went through the most critical period of the winter campaign with an extraordinarily low noneffective rate due to respiratory disease.

Actually, the prediction was based on fairly sound epidemiological and immunological reasoning. It has been demonstrated that considerable immunity is left by epidemic influenza and that outbreaks of the interpandemic type occur at least 2 years apart. The delay in appearance of influenza in 1943 deflected what would have been an almost intolerable extra burden in 1945 at a time when medical facilities were badly strained.

Observations made by English investigators[31] on the behavior of the influenza viruses may be briefly summarized, as follows: Although no epidemic occurred in the winter of 1943, a few sporadic cases of influenza showed rise in antibody titer to influenza B. In the spring and summer, a few cases were noted with influenza A. This is a very unusual time for

[31] Stuart-Harris, C. H., Glover, R. E., and Mills, K. C.: Influenza in Britain, 1942-43. Lancet 2: 790-793, 25 Dec. 1943.

finding evidence of influenza A infection. Then when the widespread epidemic took place in November, influenza A was incriminated in many sections of the country.[32]

Influenza in the U.S. Army paralleled this disease in the British civilian population. The incidence of all respiratory infections in the U.S. Army in the European theater reached a sudden peak in November 1943, with almost as rapid a fall to a point somewhat above the preepidemic level, and a subsequent slower decline through the winter months. By June, at the time of the invasion, the incidence was extremely low, and it remained low, with much less than the expected seasonal upturn, through the winter of 1945.

The great bulk of the cases on which this curve is based fall into the category called common upper respiratory infection. That the striking peak of November 1943 represents superadded influenza is presumed because of the explosive character of the epidemic, its clinical features, and serological evidence. Tests were not done on a large scale in the Army, but a sufficient number of sera from different parts of the country were examined to show that the Army experience was quite similar to British civilian experience; that is, a majority showed a rise in titer to influenza A virus.

In the Army, as with civilians in England and elsewhere, all influenza encountered during World War II was mild and uncomplicated. The patients were moderately, not severely, prostrated, and the disease was a short one with a febrile course of 2 or 3 days. To all intents and purposes, pneumonia did not occur. Influenzal pneumonia of the 1918 type was not seen. A reported increase in civilian deaths in England was found by the Ministry of Health to be due to an increased mortality caused by such conditions as congestive heart failure, associated with the general rise in the respiratory disease rate. In the U.S. Army, no deaths were attributed to influenzal pneumonia. A few complications, such as otitis and sinusitis were observed, but they were not conspicuous.

As for the clinical features of the epidemic, the familiar symptoms were encountered in many cases. However, the writer was more impressed with the widespread character of the disease than by its uniformity of behavior. As he had observed in other epidemics of influenza, a typical case was hard to define. For example, at an airbase in East Anglia in November 1943, a large number of patients were treated, but many of these had persistent colds caught on their recent transport voyage, and common upper respiratory disease confused the picture of sudden outbreak of influenza.

Mediterranean theater

Maj. (later Lt. Col.) Daniel W. Myers, MC, and Capt. (later Lt. Col.) Edward deS. Matthews, MC, stated in their report on respiratory diseases

[32] Andrewes, C. H., and Glover, R. E. Influenza "A" Outbreak of October December, 1943. Lancet 2: 104 105, 22 July 1944.

in the Mediterranean theater: "Influenza was reported 11,094 times in MTOUSA, thus apparently making up 5.9 percent of common respiratory infections; however, it is doubtful whether true influenza was encountered in MTOUSA."[33] The authors mention the fallacy of making the diagnosis solely upon clinical criteria, as the same symptoms occurred in other diseases, such as sandfly fever, malaria, and hepatitis, prevalent in the theater. There were no reports of geometric increase in frequency of influenza-like respiratory disease from any organization in this theater and incidence of acute common respiratory diseases remained within expected seasonal range. Because of lack of sufficient indication, influenzal virus studies were not attempted on a large scale. It is noteworthy, however, that by far the highest peak for the annual rate of common respiratory disease (nearly 300) occurred in January 1944 only very slightly after the epidemic of influenza A in England and the United States. It seems unlikely that the Mediterranean theater should have completely escaped so widespread a visitation, and superadded influenza would be a logical explanation for the shape of the curve at that time.

Other oversea theaters

Reported admission rates for influenza in the China-Burma-India theater and the Pacific areas were low throughout the war, and the curves for common respiratory infection show no peaks suggestive of the superadded effect of influenza.

So the history of influenza during World War II stands in happy contrast to that of World War I. Pandemic influenza did not occur. Owing to the prolongation of the epidemic cycle in the middle of the war, only one important outbreak took place and that at a time when it could be handled with ease.

PRIMARY ATYPICAL PNEUMONIA

Introduction

The term "primary atypical pneumonia" would have evoked polite incomprehension in the average medical practitioner about 20 years ago, and today it is one of our commonest diagnoses.

Pneumonias were originally classified on an anatomical basis; this was followed by a combined anatomical-clinical approach and, also, by an endeavor to identify them etiologically. These three phases were often harmonious. Thus, the common type of pneumonia appearing as a primary disease was lobar in distribution; it had well-defined clinical characteristics, and it was due to the pneumococcus. Therefore, "lobar pneumonia" was designated an anatomical, clinical, and etiological entity. As the identifica-

[33] See footnote 16, p. 8.

tion of pneumococcus types became more exact, the qualification "type I lobar pneumonia" or "type VII lobar pneumonia" was added.

Apart from the disruption of the pattern caused by the 1918 pandemic of influenza, lobar pneumonia had maintained a fairly consistent record for many years in the temperate zones as primarily a winter disease with a usual mortality of about 30 percent in cases not specifically treated. It had been subjected to exhaustive research, and a great deal of knowledge had been accumulated as to the mechanisms of recovery and immunity. The biology of the pneumococcus was, perhaps, better understood than that of any other micro-organism. By 1938, specific therapeutic sera had been produced for more than 30 types of pneumococcus.

"Bronchopneumonia" was also originally an anatomical term, but the classification of bronchopneumonias clinically was much less clearly defined. They formed a heterogeneous group. It was known that a number of micro-organisms besides the pneumococcus could cause pulmonary consolidation of peribronchial distribution. Most of these pneumonias, however, were secondary; that is, they occurred as complications of other diseases or surgical operations and in the aged and debilitated. Primary bronchopneumonias were recognized, but generally speaking they were relatively uncommon. Occasionally, the hemolytic streptococcus gave rise to primary bronchopneumonia, either in sporadic cases or in localized epidemics, when it often followed in the wake of measles or epidemic milkborne sore throat. One type of virus pneumonia, psittacosis, was recognized, but was admittedly rare. As for influenzal pneumonia, this, to all intents and purposes, had vanished after the 1918–20 pandemic.

In 1938, two events occurred to change the clinical concept of pneumonia. In the first place, in England, a chemotherapeutic agent, M. & B. 693 or sulfapyridine, was introduced which was highly effective against pneumococcal infections. Intense interest was manifested in whether sulfapyridine would supplant serum therapy as the treatment of choice in lobar pneumonia and if it would constitute a successful treatment of the bronchopneumonias. At almost the same time, an increasing number of primary pneumonias, apparently not caused by the pneumococcus and quite obviously not susceptible to chemotherapy, were being observed. A new disease entity was rapidly suspected.

The principal characteristics of this disease were as follows: It seemed to have a predilection for young adults; the onset was rather gradual; the pulmonary consolidation was patchy and often showed a migratory tendency; there was no associated leukocytosis (at least in the early stages), and the bacterial flora of the sputum was not different from that found in normals; some patients were gravely ill but after a variable febrile period complete recovery took place, with a very low overall mortality; and such slight histological material as was available indicated that the process was an interstitial pneumonitis with a mononuclear type of exudate. *Strepto-*

coccus viridans was at first thought to be the cause, but this hypothesis failed to be substantiated. With no evident bacterial etiology, the disease was then presumed to be due to a filterable virus.

But was it a new disease? Hospital clinical records between 1922 and 1935 contain infrequent descriptions of single cases exactly corresponding with the description just cited. Furthermore, beginning about 1933, occasional notations in medical literature indicate that some observers were aware of benign bronchopulmonary infiltrations simulating tuberculosis, and localized epidemics of an influenza-like disease associated with mild pneumonitis had been described. It is likely that both of these conditions were caused by the same agent or agents of the "new disease." Atypical pneumonias more or less conforming to the same description were likewise described as occurring during the winter of 1917–18.[34] The following factors probably caused the delay until 1938 in general recognition of primary atypical pneumonia: The more numerous and severe cases observed in that year, the more exact bacteriological diagnosis of the familiar types of pneumonia, and the introduction of the new chemotherapeutic agents.

Most of the increasing number of papers on primary atypical pneumonia during the ensuing years were clinical descriptions, but the research work was going forward. Broadly speaking, it is now generally agreed that atypical pneumonia is caused by a virus but by far the majority of cases are not due to the identifiable viral agents, such as psittacosis, ornithosis-lymphogranuloma, and rickettsia. Endeavors to transmit the agent to laboratory animals, or to cultivate it, have been, on the whole, disappointing. The most important studies of the etiology of primary atypical pneumonia were performed during World War II by the Commission on Acute Respiratory Diseases under the direction of Dr. Dingle. Briefly, these studies were as follows:

The disease was successfully transmitted from man to man by bacteria-free filtrates under conditions of quarantine.[35] A minority of those inoculated developed atypical pneumonia, but others had less severe illnesses which might be called bronchitis or common upper respiratory infection. In other words, there is evidence that under epidemic conditions the virus may produce many cases of nondescript respiratory infection for each one of frank atypical pneumonia. Under experimental conditions, the incubation period was not quite so long as the 2 or 3 weeks which had been estimated from epidemiological studies of the naturally occurring disease.

Two serological reactions which develop during convalescence from atypical pneumonia in the majority of cases have been discovered. One of

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[34] See footnote 1, p. 1.

[35] (1) Commission on Acute Respiratory Diseases: Transmission of Primary Atypical Pneumonia to Human Volunteers. J.A.M.A. 127: 146–149, 20 Jan. 1945. (2) Commission on Acute Respiratory Diseases: The Present Status of the Etiology of Primary Atypical Pneumonia. Bull. New York Acad. Med. 21: 235–262, May 1945. (3) Commission on Acute Respiratory Diseases: An Experimental Attempt to Transmit Primary Atypical Pneumonia in Human Volunteers. J. Clin. Investigation 24: 175–188, March 1945.

these phenomena is the cold hemagglutinin;[36] the other is the agglutinin for a certain strain of nonhemolytic streptococcus.[37] These two agglutinins are not identical, and their significance is not clear. There is general agreement that the particular streptococcus in question is not the cause of the disease.

Experience in the Continental United States

The concept of atypical pneumonia was still a fairly new one in the winter of 1941, and while the disease was recognized in most university clinics, it was not familiar to the profession as a whole. In the summer of 1941, something in the nature of a mild epidemic of pneumonia which did not respond to sulfonamide therapy occurred in southern training camps. At the request of the surgeon, Fourth Corps Area, a small civilian mission[38] was dispatched in October to several southern training camps, notably Camp Claiborne, La. It reached the conclusion that this was an epidemic of atypical pneumonia. The Surgeon General accepted a recommendation from this mission that a permanent commission be instituted for the study of the disease, inasmuch as the Army seemed an ideal milieu for such a study. This commission, established in December 1941, continued to work throughout the war, first at Camp Claiborne, and later at Fort Bragg. It conducted intensive clinical and scientific researches on the subject of atypical pneumonia, as well as other acute respiratory infections.[39] Among many noteworthy accomplishments of the Commission on Acute Respiratory Diseases were the successful human transmission experiments.[40]

The characteristics of the disease as originally seen at Camp Claiborne were briefly described by the chief of medical service of the station hospital and two of his colleagues.[41] They reported that 262 cases occurred during a period of 4 months with a camp population of about 27,000. In general, these cases were mild with a short febrile course. A few more severe cases

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[36] (1) Peterson, O. L., Ham, T. H., and Finland, M.: Cold Agglutinins (Autohemagglutinins) in Primary Atypical Pneumonias. Science 97: 167, 12 Feb. 1943. (2) Turner, J. C.: Development of Cold Agglutinins in Atypical Pneumonia. Nature, London 151: 419-420, 10 Apr. 1943.

[37] Thomas, L., Mirick, G. S., Curnen, E. C., Ziegler, J. E., Jr., and Horsfall, F. L., Jr.: Serological Reactions With Indifferent Streptococcus in Primary Atypical Pneumonia. Science 98: 566-568, 24 Dec. 1943.

[38] Drs. A. R. Dochez and Y. Kneeland, Jr., of the College of Physicians and Surgeons, Columbia University, New York, N.Y., and Dr. Colin M. MacLeod, of the New York University College of Medicine, New York, N.Y., all members of the recently created Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army.

[39] (1) Dingle, J. H., Abernethy, T. J., Badger, G. F., Buddingh, G. J., Feller, A. E., Langmuir, A. D., Ruegsegger, J. M., and Wood, W. B., Jr.: Primary Atypical Pneumonia, Etiology Unknown. War Med. 3: 223-248, March 1943. (2) Commission on Acute Respiratory Diseases: Epidemiology of Atypical Pneumonia and Acute Respiratory Disease at Fort Bragg, North Carolina. Am. J. Pub. Health 34: 335-346, April 1944. (3) Dingle, J. H., Abernethy, T. J., Badger, G. F., Buddingh, G. J., Feller, A. E., Langmuir, A. D., Ruegsegger, J. M., and Wood, W. B., Jr.: Primary Atypical Pneumonia, Etiology Unknown. (Parts I, II, and III.) Am. J. Hyg. 39: 67-128, January; 197-268, March; 269-336, May 1944. (4) Dammin, G. J., and Weller, T. H. (in collaboration with Commission on Acute Respiratory Diseases): Attempts to Transmit Primary Atypical Pneumonia and Other Respiratory Tract Infections to the Mongoose. J. Immunol. 50: 107-114, February 1945.

[40] See footnote 35, p. 18.

[41] Moore, G. B., Jr., Tannenbaum, A. J., and Smaha, T. G.: Atypical Pneumonia in an Army Camp. War Med. 2: 615-622, July 1942.

were noted, and two patients died, although there was some question of the diagnosis in one of them. Men over 28 years old were being released from the Army at this time. Occasionally, the routine predischarge X-ray in these individuals showed areas of infiltration resembling tuberculosis which cleared up quite rapidly. This, taken together with the human transmission experiments just cited, suggests that there were probably many "walking cases" of the disease. The rate of 262 cases in 27,000 troops over a period of 4 months may thus not indicate the true communicability. That it may be quite high under special circumstances is indicated by an occasional report. For example, on one occasion about 40 percent of the men out of a single company engaged as "cleanup teams" in a wire operations school contracted the disease.[42]

Shortly after the Commission began its activities, a change in terminology of the pneumonias was made by The Surgeon General, so that thenceforward primary atypical pneumonia was reported as such.[43] Clinical recognition of the disease became increasingly accurate in many hospitals, although there is reason to believe that the officially reported incidence was always low. A perusal of the large number of papers submitted to The Surgeon General to be approved for publication convinces one that the clinical characteristics of the disease were fairly uniform. The student is referred to the original articles[44] published by the Commission on Acute Respiratory Diseases for the best account of the manifestations and epidemiology of the disease.

The annual incidence of primary atypical pneumonia in Army camps throughout the war was remarkably constant. The highest admission rate in the United States (8.95 per annum per 1,000 average strength) occurred in 1943, although the validity of this may be questioned owing to change in diagnostic criteria. Seasonal variations in admission rates were more marked; with striking exceptions, rates were usually higher in the winter months. Generally speaking, cases of atypical pneumonia showed an immense numerical preponderance over lobar pneumonia, rates for which were exceedingly low. One report, from Truax Army Air Field, Madison, Wis., gives this ratio as approximately 10:1. At Scott Field, Belleville, Ill., 738 cases of atypical pneumonia were seen during a period when 24 lobar pneumonias and 37 bacterial bronchopneumonias occurred.[45] At Jefferson Barracks, Mo., 1,862 cases of atypical pneumonia were described as contrasted with 62 lobar pneumonias occurring over the same period of time.[46] These

[42] Idstrom, L. G., and Rosenberg, B.: Primary Atypical Pneumonia. Bull. U.S. Army M. Dept. No. 81, pp. 88-92, October 1944.

[43] Circular Letter No. 19, Office of the Surgeon General, U.S. Army, 2 Mar. 1942.

[44] See footnote 39 (1), (2), and (3), p. 19.

[45] Owen, C. A.: Primary Atypical Pneumonia. An Analysis of 738 Cases Occurring During 1942 at Scott Field, Ill. Arch. Int. Med. 73: 217-231, March 1944.

[46] Van Ravenswaay, A. C., Erickson, G. C., Reh, E. P., Siekierski, J. M., Pottash, R. R., and Gumbiner, B.: Clinical Aspects of Primary Atypical Pneumonia: A Study Based on 1,862 Cases Seen at Station Hospital, Jefferson Barracks, Missouri, from June 1, 1942 to August 10, 1943. J.A.M.A. 124: 1-6, 1 Jan. 1944.

cases of atypical pneumonia were said to be more severe than the average thus far described in the Army. Two deaths resulted. Pleural effusions appeared in 9.7 percent of cases; about one-quarter of these were large.

Between 1942 and 1945, 110,133 admissions for primary atypical pneumonia were reported in the Army in the United States with 101 deaths as compared to 50,807 admissions and 69 deaths overseas. Atypical pneumonia was never of sufficient magnitude to interfere seriously with the huge training program. On the other hand, the rather prolonged course of the disease and the lengthy convalescence often affected the military career of the individual concerned. Because of the rarity of complications and late sequelae, chronic invalidism did not occur.

Experience Overseas

European theater

During the late summer and autumn of 1942, there was a mild epidemic of atypical pneumonia among U.S. troops in the European theater. The incidence of lobar pneumonia was very low: in one hospital, for example, during one of the autumn months, the chief of medical service reported 3 cases which might be called typical pneumonia and 70-odd cases which were atypical. As in cases described in the States among military personnel, these cases were milder on the average than those presented in earlier reports from civilian hospitals. The febrile course was shorter, being perhaps 5 to 7 days instead of 10 to 12, and the tendency to relapse, or prolonged migratory pneumonia, was much less pronounced. Moreover, such bizarre manifestations as erythematous skin lesions, liver involvement, pericarditis, and so forth, which had been noted on rare occasions in civilian outbreaks, were not observed. A true pleuritic pain, so commonly found in lobar pneumonia, is not a feature of atypical pneumonia. Sterile pleural effusions may occur; when they do, they are usually small and often interlobar. Occasionally, however, they may persist for an appreciable period, and in 1942 when this was so they were conventionally considered highly suggestive of tuberculosis It was pointed out then that a small effusion need not be regarded as tuberculous, and where there was any evidence of associated pneumonitis, past or present, atypical pneumonia was probably the cause.

In the autumn of 1942, a board composed of an epidemiologist, Lt. Col. (later Col.) John E. Gordon, MC; a clinician, Lt. Col. (later Col.) Yale Kneeland, Jr., MC; and a virologist, Maj. (later Col.) Ralph S. Muckenfuss, MC, was appointed to consider the subject of atypical pneumonia. The results of its deliberations were embodied in a circular letter, which outlined the history and clinical features of atypical pneumonia, together with advice as to management. It was pointed out that sulfonamides were ineffective in this disease and that, if the diagnosis could be made with reasonable certainty by a mature clinician with an adequate laboratory at his disposal, sulfonamides were contraindicated. Where the diagnosis was in doubt, or

satisfactory laboratory facilities unavailable, sulfonamides in full dosage were recommended for a brief but definitive therapeutic trial. Attention was drawn to the possibly prolonged residual effects of an attack of atypical pneumonia and to the need for a considerable rehabilitation before the soldier returned to duty.

During the winter and summer of 1943, atypical pneumonia was less conspicuous. The phenomenon of cold hemagglutination was described and carefully reported in relation to a fairly large series of cases by a medical officer in the European theater almost simultaneously with independent discovery of the phenomenon in the United States.[47] Rare cases of encephalitis complicating the pulmonary lesions were encountered in the theater. In one fatal case, histological evidence was found at autopsy.[48] In two others, encephalitis was recognized clinically from symptoms and spinal fluid findings.[49]

Atypical pneumonia was not generally recognized by the bulk of the British medical profession in 1942, although scientific investigators were aware that a form of pneumonia, presumably of viral origin, had recently come into prominence in America. Contacts between British investigators and American medical officers were soon established. Professor Bedson,[50] for example, tested serum from several convalescent U.S. soldiers for antibodies to psittacosis virus with negative results. Dr. C. H. Andrewes tested sera for antibodies to influenza virus, similarly with negative results. The possibility that pigeons imported by the U.S. Army Signal Corps might introduce an ornithosis-like disease in humans into the British Isles seemed remote when it was found that native British birds were already infected.[51] It seems highly unlikely that atypical pneumonia was brought into the British Isles de novo by the U.S. Army. In fact, ward rounds in any British Army hospital in the autumn of 1942 convinced one that the disease in a mild form was present. Stimulated in part by American interest in the disease,[52] British physicians shortly began to recognize it, and in 1943 an excellent descriptive article[53] appeared in the *Lancet*.

In the autumn of 1943, at a second meeting of the Atypical Pneumonia Board (p. 21), it was recommended that routine cold agglutinin tests be performed in hospitals, that careful records be kept, that a summary be made of the results of the test in a large series of cases, and that informa-

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[47] See footnote 36 (1), p. 19.

[48] Perrone, H., and Wright, M.: Fatal Case of Atypical Pneumonia With Encephalitis. Brit. M.J. 2: 63–65, 17 July 1943.

[49] Hein, G. E.: Primary Atypical Pneumonia. Lancet 1: 431-432, 3 April 1943.

[50] Sir Sam Phillips Bedson, M.D., F.R.C.P., F.R.S., Consulting Advisor in Pathology, Ministry of Health.

[51] Andrewes, C. H., and Mills, K. C.: Psittacosis (Ornithosis) Virus in English Pigeons. Lancet 1: 292-294, 6 Mar. 1943.

[52] Brown, J. W., Hein, G. E., Ellman, P., and Joules, H.: Discussion on Atypical Pneumonia. Proc. Roy. Soc. Med. 36: 385–390, June 1943.

[53] Drew, W. R. M., Samuel, E., and Ball, M.: Primary Atypical Pneumonia. Lancet 1: 761–765, 19 June 1943.

tion be obtained as to the frequency of second attacks. Some data were collected, but no important conclusions could be drawn.

The annual admission rate in the European theater for primary atypical pneumonia was 9.23 in 1942, 6.35 in 1943, and only 4.80 in 1944. Apart from the late summer-autumn peak of 1942, these rates were considerably lower than in the United States. This may be partly ascribed to the fact that the virus of atypical pneumonia seems to have been less widespread and virulent in England than in the United States. Seasoning of troops might have played a role also, but one is inclined to doubt that it was very large, since rates in the Mediterranean theater, where the troops were also seasoned, were much higher than at home for the years 1944 and 1945.

An interesting observation was made in the winter of 1945 at the 7th General Hospital in Dorsetshire, England. Two patients were studied who showed extremely high cold agglutinin titers with associated hemolytic crises. One of these episodes followed a definite attack of atypical pneumonia. This phenomenon has since been discussed in considerable detail by Finland and his coworkers.[54]

Mediterranean theater

Available statistical reports in the Mediterranean theater do not provide a reliable indication of the relative frequencies of lobar and atypical pneumonia before May 1944. From 1 May 1944 to 31 March 1945, inclusive, 7,142 primary pneumonias were reported, of which 5,684, or approximately 80 percent, were classified as atypical pneumonia.[55] If this percentage holds for the entire history of the theater, it would seem that the preponderance of atypical pneumonias over bacterial pneumonias was less than in some other areas.

The general situation in regard to pneumonia in the Mediterranean theater as reported in 1945 (p. 8) is described in the following paragraph:

> The pneumonia rate in the theater remained at comparatively low levels until January 1944 when a marked increase was noted principally in the troops based in Italy. This increased incidence was manifested by both Base Section and Army troops, the peak level for this season occurring in the Peninsular Base Section during April 1944 when the rate was 38.5 per 1,000 per annum. The rate in Italy remained high until July, the incidence in Army falling more precipitously and at an earlier date than in the Base. In January 1945 a similar rise in pneumonia rates began, the rate in March 1945 reaching a level substantially higher than that in the preceding year. Peninsular Base Section and Fifth U.S. Army troops participated in the rise, and once more the incidence was highest in the Base, attaining the surprising level of 82 per 1,000 per annum in the month of March. It is of interest, though an explanation is not offered, that pneumonia in the Army Air Forces reached its height in February 1945 and fell precipitously in March when Fifth U.S. Army and Peninsular Base rates were still ascending. The case fatality rates showed

[54] Finland, M., Peterson, O. L., Allen, H. E., Samper, B. A., and Barnes, M. W.: Cold Agglutinins. I. Occurrence of Cold Isohemagglutinins in Various Conditions. II. Cold Isohemagglutinins in Primary Atypical Pneumonia of Unknown Etiology With a Note on the Occurrence of Hemolytic Anemia in These Cases. J. Clin. Investigation 24: 451-457; 458-473, July 1945.

[55] See footnote 16, p. 8.

a fall rather than a corresponding rise in the years of greatest incidence. In 1943, 24 deaths occurred in 1,427 pneumonias, a case fatality rate of 1.68 percent. There were 7,489 pneumonias and 35 deaths in 1944, a rate of 0.47 percent. During the first 3 months of 1945, 3,263 pneumonias and 6 pneumonia deaths were encountered, a case fatality of 0.18 percent. The quoted rates included all pneumonia deaths.

If 80 percent of the pneumonia was atypical its incidence was at times very high.

Clinical descriptions of the disease in the Mediterranean theater were generally similar to those published elsewhere. However, several peculiar outbreaks occurred which excited a good deal of interest and were the subject of considerable investigation. The report of Myers and Matthews (p. 8) described these in some detail. One took place in an isolation ward of the 24th General Hospital in the Bizerte area, Tunisia, in the winter of 1943–44. Within a 9-day period, over half the patients and ward personnel (13 in all) contracted mild atypical pneumonia. A tentmate of one of the affected aidmen and a substitute aidman also became ill, the latter 6 days after the first contact. The outbreak appeared to have an unusually short incubation period and a high degree of communicability. Its origin could not be traced.

During the 1944–45 pneumonia season, seven local outbreaks occurred. One, of 82 cases in the personnel of one company, arose in Corsica in December 1944, and the remaining six outbreaks occurred between December and April in separate organizations in a 5-mile radius of North Central Italy. The Corsican cases were as follows:

* * * The usual duration of fever was five days, maximum temperature varying from 100° to 105°, and recovery without serious complications ensued in every case. Diagnosis was established by chest X-ray examination in nearly every instance. Two hundred cold agglutination tests were performed by Capt. Joseph H. Swartz, utilizing the sera from the 82 patients and a 2 percent suspension of washed human group O erythrocytes. In two cases agglutination was observed with a serum dilution of 1:32. In the remainder agglutination did not occur with serum titer greater than 1:8. There were no circumstances incriminating an insect vector.

The extremely high attack rate and the negative cold agglutinin tests suggest that this was not primary atypical pneumonia. The same report gives a description of four localized, sharp epidemics occurring near Pagliana, Italy, and totaling at least 355 cases. These constitute additional evidence of the existence in Italy of a specific and different disease entity. One of the involved units had an attack rate of 27.7 percent. The disease characteristically had an abrupt onset, with an incubation period apparently varying from 17 to 23 days. Cold agglutinins were not found, and it was suspected that the etiological agent might have had an insect vector, a mite, which was found in large numbers in the area used by one of the units involved.

Two more outbreaks, totaling 53 cases, occurred about 10 airline miles north-northeast of Pagliana. These cases again differed in certain noteworthy respects from atypical pneumonia: that is, abruptness of onset, fre-

quent appearance of pleuritic pain, and absence of cold agglutinins. Complement fixation tests performed with lymphogranuloma antigen on both human and pigeon serum (from the area) were negative for psittacosis, as were other serological tests (Weil-Felix, influenza A and B, cold agglutinin). Attempts at virus isolation were also made. Preliminary observations suggested that throat washings from acute cases contained a filterable agent which produced fever on guinea pig inoculation and was transmissible in series. A rickettsial agent was finally isolated from the material. Moreover, late followup serological tests on other cases of the disease which developed in troops returning from Italy have shown that the condition was, in fact, Q fever. It seems definitely proved that all the above cases as well as the so-called Balkan grippe occurring among British paratroopers in Greece were Q fever.[56]

Myers and Matthews noted that true atypical pneumonia in Italy during the winter of 1943–44 took on a rather more severe character than they were accustomed to observe in Army practice. There was a large number of severe cases, reminiscent of those described in the United States in 1938, with cyanosis, dyspnea, and extensive pulmonary involvement. Some of these ended fatally. Another group showed a protracted course, with persistence of pulmonary infiltration beyond the expected period. In one group,[57] 55.8 percent of cases had residual X-ray changes after 3 weeks of illness.

Lt. Col. Tracy B. Mallory, MC, of the 15th Medical General Laboratory, furnished the following description of his findings in the tissues of nine fatal cases:[58]

> Each of the nine cases showed consolidation of more than 75 percent of the total lung substance. Microscopic examination disclosed massive exudation into the alveoli of a protein-rich fluid, almost free of fibrin, and containing mononuclear and red cells but few polymorphonuclear leukocytes. Alveolar wall thickening was observed but was minor in degree. In no case was there evidence of necrotizing bronchiolitis or atelectasis, lesions characteristic of the atypical pneumonia seen in troops in the continental United States during 1942–43. A serous or purulent effusion was not found in any instance.
>
> Four of the nine evidenced other pathological changes unrelated to the pneumonia but of such character and degree as to have contributed to the fatal issue. One exhibited recent vegetations superimposed on an old rheumatic valvulitis, the second had a fresh myocardial infarction, the third a hemoperitoneum associated with a fractured pelvis, and the fourth a fracture of the dorsal spine with paraplegia. Three other cases displayed a well-marked acute myocarditis which was deemed to be a complication of the pneumonia and which undoubtedly played an important part in the outcome.

Summary

In summary, primary atypical pneumonia was by far the most common variety of pneumonia in U.S. troops in the European and Mediterranean

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[56] Commission on Acute Respiratory Diseases: Outbreaks of a Rickettsial Disease Related to Q Fever. Bull. U.S. Army M. Dept. 5 (No. 3): 245–246, March 1946.

[57] Theodos, P. A., and Zwickel, R. E.: Clinical Aspects of Primary Atypical Pneumonia. M. Bull. North African Theater Op. 2: 104–109, November 1944.

[58] See footnote 16, p. 8.

theaters. Even so, it never became a military medical problem of any real importance. Rates for Europe were lower than in the continental United States, but in the Mediterranean they were sometimes higher. On the whole, the cases were mild and recovery tended to be complete, although an average of about 30 days per patient were lost to duty. Very rarely, the individual might be left with a chronic bronchitis, sometimes of an asthmatic type. Secondary bronchiectasis was almost unknown. Complications were very infrequent. A few of the patients at times seemed to have some secondary bacterial infection. Such secondary infections were usually not very clear cut, but when definite they were controlled by sulfonamides. The death rate was almost nil.

Had the incidence of this condition been higher, it would have been a military problem of some magnitude owing to the rather prolonged disability incurred by the individual. This low incidence probably reflects a considerable degree of immunity in the general population. The virus, too, may be one of rather low communicability, and the long incubation period militates against the explosive type of epidemic spread when individuals are temporarily crowded together, as on transports.

Rates for atypical pneumonia were low throughout the war in the Pacific area. They were also low in the China-Burma-India theater apart from a moderate peak in July and August 1942. In the latter area, the disease picture was stated to conform with that seen in the United States except that an initial shaking chill and pleuritic pain were more commonly encountered.

An interesting outbreak, late in 1944, was described by the surgeon of an airbase in India. Fourteen persons, all of whom had been in the same hold of a troop transport arriving in Bombay, came down with atypical pneumonia almost simultaneously a few days afterward. About a fortnight later, there were eight secondary cases at the station.

BACTERIAL PNEUMONIA

Introduction

Lobar pneumonia due to the pneumococcus has been so closely studied and so accurately described that it would be presumptuous to review the disease here. Medical records indicate a total of 109,882 admissions for pneumonia other than atypical as occurring in the Army from 1942-45 (table 2). Of these, 970 patients died, giving a case fatality rate of 0.88 percent. This is in contrast to a figure of 160,940 admissions for atypical pneumonia with 198 deaths. How many of these reported cases were actually pneumococcal pneumonia is impossible to state; probably the percentage was a relatively small one. Two generalizations may be made concerning the condition in World War II. First, the incidence was generally lower than anticipated, particularly overseas. This low rate was simultaneously true of the civilian population and probably reflects an inexplicable fluctuation in the character

of the disease which had begun some years before World War II. Secondly, and perhaps for the same reason, the individual cases seemed surprisingly mild. One is accustomed to think of lobar pneumonia beginning violently in the classical way, with a rapid development of the complete picture of the disease and bacteremia in about 25 percent of the cases. In the Army, the disease did begin suddenly with the customary symptoms, but the patient usually did not appear as ill as one might expect; the amount of consolidation by X-ray was often astonishingly slight, and bacteremia was extremely uncommon. It is possible that these differences were apparent rather than real, that they were due to prompt recognition and early treatment. Nevertheless, it is the writer's belief that the essential severity of the disease was diminished.

Other varieties of primary bacterial pneumonia were rarely encountered. On the extremely infrequent occasions in which organisms, such as *Staphylococcus*, *Friedländer's bacillus*, and *H. influenzae*, produced pneumonia, they ran true to form. Secondary pneumonias, usually on the surgical wards, were occasionally noted, but on the whole the control of these conditions by antibiotics was satisfactory.

TABLE 2.—*Admissions for primary atypical pneumonia, bacterial pneumonia, and other pneumonia, in the U.S. Army, by area and year, 1942–45*

[Preliminary data based on sample tabulations of individual medical records]
[Rate expressed as number of admissions per annum per 1,000 average strength]

Disease category and year	Total Army		United States		Overseas	
	Number	Rate	Number	Rate	Number	Rate
Primary atypical pneumonia:						
1942–45	160, 940	6. 32	110, 133	7. 47	50, 807	4. 73
1942	19, 891	6. 13	17, 902	6. 74	1, 989	3. 40
1943	51, 177	7. 45	46, 375	8. 95	4, 802	2. 84
1944	43, 022	5. 52	25, 056	6. 31	17, 966	4. 70
1945	46, 850	6. 18	20, 800	7. 09	26, 050	5. 61
Other pneumonia:						
1942–45	109, 882	4. 31	81, 962	5. 56	27, 920	2. 60
1942	27, 583	8. 51	24, 267	9. 13	3, 316	5. 66
1943	41, 161	5. 99	35, 735	6. 90	5, 426	3. 21
1944	23, 473	3. 01	14, 470	3. 64	9, 003	2. 36
1945	17, 665	2. 33	7, 490	2. 55	10, 175	2. 19
Bacterial pneumonia: [1]						
1942–45	50, 943	2. 00	37, 406	2. 54	13, 537	1. 26
1942	10, 441	3. 22	9, 340	3. 52	1, 101	1. 88
1943	16, 838	2. 45	14, 690	2. 83	2, 148	1. 27
1944	13, 014	1. 67	8, 526	2. 15	4, 488	1. 18
1945	10, 650	1. 41	4, 850	1. 65	5, 800	1. 25

[1] Cases recorded as lobar pneumonia.

The hemolytic streptococcus gives rise to an occasional case of primary pneumonia; however, the cases become numerically important only when for some reason the organism is widely distributed in a highly pathogenic state, as is sometimes found in association with a milkborne epidemic. Measles and influenza viruses seemed to "activate" the hemolytic streptococcus in the First World War but during the Second World War measles was unimportant in the Army and influenza of the 1918 type did not occur. These facts probably are related to the low incidence of streptococcal pneumonia. What effect did the widespread use of sulfonamides have in preventing the streptococcus from really getting under way? This complex subject will be considered elsewhere, together with that extraordinarily interesting phenomenon, the appearance of sulfonamide-resistant strains of beta hemolytic streptococci.

Experience in the Continental United States

On summary health reports, statistical data in the Army with regard to the pneumonias are unsatisfactory. After March 1942, the pneumonias were reported under three headings: Primary atypical pneumonia; pneumonia, primary; and pneumonia, secondary. The rates for pneumonia, secondary, were generally very low. Our interest here is in the term "pneumonia, primary."

By definition, this should mean any pneumonia arising de novo, or in the course of minor upper respiratory infection, which a medical officer considers to be bacterial, not viral, in origin. Presumably, these should be mainly pneumococcal, that is to say, lobar pneumonia. As might be expected, medical records based on the consolidated statistical health report (WD MD Form 86ab) contain an enormous amount of error, resulting from the natural limitations of this source of information.

For example, at Camp Lee, Va., between 6 November 1943 and 3 March 1944, 155 cases of pneumonia were reported; 147 designated pneumonia, primary, and 8 atypical pneumonia. This seemed of sufficient interest to warrant further investigation. The Director, Commission on Pneumonia, Army Epidemiological Board, visited Camp Lee and studied records on 97 pneumonia cases admitted since 1 January 1944. In his opinion, 58 of these were atypical pneumonia, and only 8 were lobar pneumonia. The remainder consisted of 6 definitely streptococcal cases, 13 doubtful streptococcal cases, 10 probably bacterial pneumonias from which no organism was isolated, and 2 staphylococcal cases.

There were several reasons for this woeful degree of inaccuracy. One, of course, was the failure of many clinicians to think clearly along etiological lines; another was lack of interest and experience on the part of the laboratory; and last, but not least, was the registrar's habit of making up the statistical health report from the morning report which was usually compiled by a nurse. There is, therefore, little to be gained from a discussion of the overall incidence of so-called pneumonia, primary, as reported on periodic

summary reports. In contrast, considerable information is made available from the tabulations of final diagnoses from individual medical records (table 2).

The low incidence and mortality of lobar pneumonia in the Army may be illustrated by two figures which, although not strictly comparable, do give a crude index of affairs. The death rate from lobar pneumonia is given in the official history of the First World War as 2.59 per 1,000 per year, or 259 per 100,000 per year, for the period 1 April 1917 to 31 December 1919. Preliminary Army figures in World War II, 1942–45, give the death rate for the bacterial pneumonia in the United States as less than 2 per 100,000 per year.

Lobar pneumonia was mildly epidemic in the United States at times, but only in certain localities. Epidemic conditions never became generalized. The most conspicuous instances of this were in the Sixth Service Command where the rates for pneumonia were significantly higher than in other service commands. These high rates were entirely contributed by Air Forces personnel, the rate for Army Service Forces being not dissimilar to that in other regions. Accordingly, the matter was investigated by the consultant in medicine of the Sixth Service Command and the director of the Commission on Pneumonia who reported a number of interesting figures. For example, rates for common respiratory disease the week of 20 October 1944 at three airfields were 150, 111, and 83 as compared to 55 and 64 in two service camps. Similarly, the pneumonia rates were 32, 41, and 55, compared to 7 and 3. These reported pneumonias included both lobar pneumonia and atypical pneumonia. The exact proportion of the two varieties was hard to determine. At one field between 1 January and 8 December 1944, 215 cases of primary pneumonia were reported as against 396 atypical pneumonia cases, but when the investigators studied the individual medical records rather than the statistical health report they found that at the three airfields primary pneumonia was being somewhat overdiagnosed at the expense of atypical pneumonia. Nevertheless, it was obvious that lobar pneumonia was unusually prevalent.

At one field, pneumococcus typings had been performed in 160 cases. In these, type VII was present in 18.1 percent of cases, types I and II each in 14.4 percent, so that these three together accounted for nearly half the cases. The prominence of type VII seems a little surprising; whether it was also such a notable offender at the other two fields is unknown.

A careful attempt was made to discover the reasons for this unusual incidence of respiratory infection including pneumonia. In the final analysis, the most striking difference between life at the air station and in the service forces was that the former involved men being together in classrooms all day.

Another interesting example of the behavior of lobar pneumonia was reported at the Army Air Force Technical School, Sioux Falls. Coincident

with the peak of a sharp epidemic of influenza in November 1943, and extending for about a fortnight afterward while the influenza was rapidly subsiding, the rate for lobar pneumonia (already rather high) rose to an unprecedented level. For the week of 3 December, it was 4.8 per 1,000. In 72 cases, pneumococci were isolated and typed. Of these, 17 proved to be type II, 9 type V, 6 type I, and 5 type VII. The rest were scattered or untypable. Later in the winter, during a controlled experiment on sulfadiazine prophylaxis at the same station, it was noted that the drug appeared to reduce significantly the incidence of lobar pneumonia, although the result was not as striking as in the case of streptococcal infections.

In harmony with all experience elsewhere, the treatment of lobar pneumonia with sulfadiazine was highly satisfactory, and complications were very infrequent. In this connection, it is interesting to review the role of serum therapy. At a conference on pneumonia held at the Office of the Surgeon General in January 1944, the subject of classification was discussed at length. Therapy was also considered, and it was agreed that antipneumococcus serum may be lifesaving in cases of drug-resistant pneumonia. Shortly thereafter, a remarkable variation in the actual use of antipneumococcus serum in various hospitals was uncovered in a survey by the Professional Service Division. A good many hospitals had never used serum while in others it had been employed surprisingly often. The opinion of all the service command consultants in medicine was then sought. The great majority agreed that serum was necessary in only very exceptional instances and that it could, if necessary, be obtained from local sources. In other words, the consensus was that antipneumococcus serum could be discontinued in the Army drug lists; in this, the Chief Consultant in Medicine, Office of the Surgeon General, and the National Research Council concurred on 15 May 1944. The advent of penicillin as an addition to sulfonamides had much to do with influencing this view, which would have been considered mildly revolutionary a few years earlier. The efficacy of treatment of lobar pneumonia with sulfonamides alone is shown by a report of 454 cases over a period of 3 years with only 4 deaths.[59] In the last year of this study, 92 cases were treated without a single death.

An important study of immunization against lobar pneumonia by injection of specific capsular polysaccharides was started in September 1944 at the Sioux Falls Army Air Force Technical School[60] where the pneumonia rate had been very high; over 1,500 cases had occurred in the preceding 2 years. Of these, 34.9 percent were due to type II pneumococcus. More than 8,000 men were injected with a single dose of a mixture containing polysaccharides derived from pneumococcus types I, II, V, and VII with a strik-

[59] Adamson, W. B.: Lobar Pneumonia. Air Surgeon's Bull. (No. 11) 1: 21, November 1944.

[60] MacLeod, C. M., Hodges, R. G., Heidelberger, M., and Bernhard, W. G.: Prevention of Pneumococcal Pneumonia by Immunization With Specific Capsular Polysaccharides. J. Exper. Med. 82: 445-465, December 1945.

ing subsequent immunity to pneumonia caused by these types as compared with a similar control group. The carrier rate of these four types was also significantly reduced, but no effect was noted against infection with, or the carrier rate of, other types.

Hemolytic streptococcal pneumonia was comparatively uncommon. Some cases were seen, however, which conformed to the pattern set in the First World War; that is, an abrupt onset of the pneumonia with symptoms of pleurisy and the rapid development of a massive effusion. Such effusions were characteristically thin but, of course, infected. The opportunity to use local penicillin therapy was seized, but the cases were not sufficiently numerous to draw any final conclusions as to its efficacy. Early in 1944, one station hospital in the Third Service Command reported 5 such cases, together with 10 other pneumonias, believed to be streptococcal, which did not have associated empyema. At about the same time, six cases were present in another hospital in the same service command. These numbers, however, were quite unusual. Other varieties of bacterial pneumonia were occasionally encountered, but not with sufficient frequency to merit particular comment.

Bacterial pneumonia never became a serious problem in the United States, and its response to sulfonamides and antibiotics completely changed its significance as compared with the First World War.

Experience Overseas

European theater

The incidence of bacterial pneumonia in the European theater was extremely low, and the mortality almost nil. This small fatality rate can be ascribed, in part at least, to early diagnosis and satisfactory response to treatment.

Empyema following lobar pneumonia was very inconspicuous in the Second World War. When it occurred, it was ordinarily the result of delay in the institution of treatment, the pneumonia at times having been unsuspected. Other complications were exceedingly rare.

The typing of pneumococci was always difficult overseas. This was no doubt in part due to lack of training of laboratory technicians. However, it also appeared to be a fact that the available typing serum was weak.

There were a number of scattered cases of bronchopneumonia in the European theater, particularly in the spring of 1944, in which the differential diagnosis between atypical and bacterial infection was in doubt. Clinically, these cases resembled atypical pneumonia, but the sputum was more purulent than one expects in that disease and contained a pathogenic organism. These cases occasionally showed a moderate, although not a dramatic, response to sulfonamides. They may have represented instances of secondary infection superimposed on a pneumonia originally of viral origin.

Mediterranean theater

Preliminary data on pneumonia in the Mediterranean theater indicate that there were 17,715 admissions for these diseases during the period 1942–45. Of these, 12,908 were reported as primary atypical pneumonia, and 2,443 (approximately 14 percent) were regarded as bacterial pneumonia. There were 74 deaths, and of these, 28 were due to bacterial pneumonia. Presumably, the bulk of the bacterial pneumonias were pneumococcal, and pneumococcal lobar pneumonia is estimated to have caused about one-third of the deaths from pneumonia that occurred in the theater.

Other types of bacterial pneumonia were occasionally noted in the Mediterranean theater but in insufficient numbers to warrant discussion. A small number of cases in which a green streptococcus was cultivated from blood and sputum are recorded. *Str. viridans* pneumonia was a clinical rarity, but had been previously observed. It is possible to speculate on the relation of this condition to atypical pneumonia, with the streptococcus in the role of secondary invader, but no proof of such relationship exists.

The standard treatment of lobar pneumonia was sulfadiazine, which yielded satisfactory results. Penicillin was tried in a limited number of cases and found to be effective. Occasionally, in a severe case, both agents were used. Serum therapy was only recommended in very exceptional cases.

MEASLES

Introduction

Measles (rubeola) is a highly communicable virus disease with a stereotyped clinical pattern which is universally familiar. Susceptibility to measles is considered to be almost universal, and one attack, in the majority of persons, confers lifelong immunity. In urban communities, it is more or less epidemic in the early spring of each year with a greater number of cases in alternate years. Approximately 102,000 cases of measles occurred in the U.S. Army in the First World War, with 2,370 deaths. Associated infections were a cause of serious illness, prolonged invalidism, and death. In World War II, by contrast, the total number of cases was 60,809, with only 33 deaths, in spite of the fact that the Army was about four times as large and the duration of the war twice as long. The seasonal peak for measles during World War II occurred in late winter or early spring, but during World War I peak incidence due to mobilization occurred in the late fall of 1917. This is of sufficient importance to warrant considerable discussion.

Uncomplicated measles is almost never fatal. The gravity of the condition lies in complications caused by certain micro-organisms. Bacterial infections due to pneumococcus, *C. diphtheriae*, *H. influenzae*, *Mycobacterium tuberculosis*, and most particularly the hemolytic streptococcus, are described.

The most frequent and serious complications of measles are pneumonia and otitis media. In the First World War, there were 93,629 admissions due

to measles among enlisted men in the continental United States and Europe of which bronchopneumonia and lobar pneumonia were complications of measles in 6,283 cases, with 2,186 deaths. Similar data for the entire Army are not available. Suppurative pleurisy, undoubtedly secondary to pneumonia, occurred in 645 cases with 268 deaths. There were 3,926 instances of otitis media, but only 122 of these patients died. Careful studies of the bacteriology of these complications indicated that the hemolytic streptococcus was the causative agent in nearly every case. One may ask how this secondary infection comes about. Does it occur in a carrier of streptococcus who becomes infected with measles? Does one catch the streptococcus along with the virus of measles or does one become secondarily infected as a result of living in a highly contaminated environment after contracting the measles? It seems likely that all these mechanisms play a part. At one hospital in the First World War, for instance, the carrier rate for hemolytic streptococcus rose steadily on measles wards from 11 percent on admission to 57 percent in patients who had been on the ward from 8 to 16 days. If noncarriers of streptococcus with measles were carefully segregated from carriers at the time of admission, the difference in complications was striking, the rate being 6.4 percent in the noncarriers as opposed to 36.8 percent in the carriers. While the mechanism of secondary infection might not always be clear in the individual case, it is safe to conclude that, during a measles epidemic in a training camp, the hemolytic streptococcus became widely distributed.

Following a measles epidemic with much complicating pneumonia, primary streptococcal pneumonia made its appearance in some camps. The cases were severe, with a high incidence of early suppurative pleurisy, and a high case fatality rate. This disease also spread to the civilian population. It seems likely that rapid passage from individual to individual through the mediation of measles enhanced the essential infectivity and virulence of the hemolytic streptococcus.

Epidemiological studies of measles in the First World War also have an interesting bearing on more recent events. In such a station as Camp Pike, Ark., which drew its recruits from the rural regions of Alabama, Arkansas, Louisiana, Mississippi, and Tennessee, the rate was enormously higher than in camps drawing from urban areas. Thus, the admission rate for measles among white enlisted men at Camp Pike was 164.67 per 1,000 per year, compared to 7.27 at Camp Dix, N.J. For white and colored enlisted men combined, the admission rates were 142.05 per 1,000 per year for Camp Pike and 7.73 for Camp Dix. Moreover, as might be expected, the incidence of measles was highest in recruits less than 2 months in camp. Thus, it was essentially a disease of country boys coming for the first time in their lives into a densely crowded environment.

The only tenable explanation of the much lower rates for measles in the Second World War is that the number of susceptibles was much smaller. There is no question that a great change in habits of life occurred in rural

America between the two World Wars. In 1910, rural districts were fairly well isolated; it was the "horse and buggy era"; the facilities of travel were limited; people stayed on the farm. By 1935, all this had changed. There was a moving picture house in nearly every village; schools were larger, and education was more centralized. As a result, the country boy growing up in this decade had far more opportunity for exposure to the exanthemata of childhood with a consequent reduction in susceptibility rate at the time of induction into the Army. Although there is no firm statistical basis for this conclusion, one cannot avoid feeling that it must be correct.

Complications of measles were much less conspicuous in World War II. Undoubtedly, this was related to the low incidence of the disease. Where cases are sporadic, rather than epidemic, the widespread dissemination of virulent streptococci is unlikely to take place. Moreover, the use of sulfadiazine in cases with threatened or actual complications unquestionably served to modify the picture. Part of the small number of deaths were probably due to secondary infection; some may have occurred as a result simply of overwhelming virus infection or complicating encephalitis.

An average of about 13 days was lost to duty for each case of measles.

Experience in the Continental United States

Most of the measles in the Army took place in the United States for the reasons just mentioned; that is, that it is essentially a disease of unseasoned troops first entering military life. Actually, 54,388 cases occurred in the United States as contrasted with 6,421 overseas. The largest number and the highest rates were reported in 1943, although in the civilian population the absolute numbers of cases were about the same in 1942, 1943, and 1944. As in the First World War, the disease was seasonal, but the peaks were much lower. In other words, while the total number of cases was considerable, measles never became a really serious military problem.

The relative insignificance of complications is illustrated by a report of 400 cases of measles at the Station Hospital, Fort Sill, Okla., in which otitis media occurred but 6 times.[61] Three hundred of these were given sulfonamides, but 100 control cases were untreated. No difference was noted in the clinical course of the treated as opposed to the control cases.

Suppression or modification of measles following exposure by the injection of convalescent serum or immune globulin are established procedures in pediatric practice. Measles in the Army, however, never was sufficiently serious to warrant the generalized use of these measures. Similarly, no attempt was made to apply the principles of active immunization, although interesting preliminary studies, under the direction of the Commission on Measles

[61] Haerem, A. T.: Treatment of Measles and Mumps With Three Well-Known Sulfonamides. Mil. Surgeon 92: 306-309, March 1943.

and Mumps, Army Epidemiological Board, indicated the immunizing value of artificially cultivated measles virus.[62]

Experience Overseas

Measles rates in the European theater were low, a total of 2,554 cases being reported. The disease was sporadic, and nothing in the nature of a real epidemic ever developed. Clinically, the cases presented no unusual features. Sulfadiazine was administered to most of the patients for several days during the acute phase. Only one death was attributed to the disease.

Between 1 January 1943 and 31 March 1945, 612 cases of measles with no deaths were reported in the Mediterranean theater.

MUMPS

Introduction

Of the so-called communicable diseases of childhood, mumps (epidemic parotitis) was the most common in the U.S. Army. There were 103,055 cases recorded between 1942–45 compared with approximately 237,000 during the First World War, for a much smaller number of men over a shorter period of time. This marked reduction was greater than that for measles, the comparable figures being 60,809 and 102,000, respectively.

No exact explanation of the reason for this is possible, but a plausible hypothesis suggests itself. As has already been pointed out in the section on measles, a change in the living habits of rural America probably permitted more exposure in childhood and resulted in fewer susceptibles of military age. Measles is more highly communicable than mumps; therefore, when measles occurs under conditions of military life, where opportunity for spread of epidemic disease is excellent, it is likely that a higher percentage of the nonimmunes will contract measles than mumps. Thus, the proportionate decline in the incidence of the two diseases during the two World Wars might be expected to be greater in measles, the highly communicable disease, than in mumps, the disease of lesser communicability.

Complications

Mumps is a specific virus infection with a particular tendency to localization in the parotid glands. In the majority of cases, these are the only organs clinically affected. However, a number of other glands and structures are ordinarily spoken of as complications, although they are probably better regarded as additional manifestations of the virus infection. Generally speak-

[62] (1) Stokes, J., Jr., O'Neil, G. C., Shaffer, M. F., Rake, G., and Maris, E. P.: Studies on Measles. IV. Results Following Inoculation of Children With Egg-Passage Measles Virus. J. Pediat. 22: 3–18, January 1943. (2) Maris, E. P., Rake, G., Stokes, J., Jr., Shaffer, M. F., and O'Neil, G. C.: Studies on Measles. V. Results of Chance and Planned Exposure to Unmodified Measles Virus in Children Previously Inoculated With Egg-Passage Measles Virus. J. Pediat. 22: 17–19, January 1943.

ing, these complications are troublesome, but not particularly serious. Mumps is essentially a nonfatal disease, and in the First World War the only deaths occurred as a result of infrequent secondary infections, such as pneumonia. At that time, the case fatality rate where mumps was the primary cause of admission was 0.08 percent. As there were only five deaths from mumps reported for the entire U.S. Army during the Second World War, it can be seen that even the cited low figure was markedly reduced.

Perhaps the most striking of these so-called complications is orchitis which develops as a rule when the parotitis is subsiding. Rarely it is said to be the only manifestation of mumps. In a recent study of the disease in civilian life, orchitis is stated to occur in 18 percent of cases of mumps, and in about one-sixth of these the condition is bilateral.[63] In over 50 percent, some atrophy is said to result, but ensuing sterility is claimed to be rare, probably because the cases are unilateral, and even in bilateral cases with atrophy a sufficient amount of spermatogenic tissue is left intact. The authors of this paper recommend surgical decompression in severe cases, a procedure which was tried at times in the Army during World War II with allegedly good results.[64] It seems likely that comparatively few cases are sufficiently severe to require such an operation. It is reported to cause remarkable relief, however, in patients with very marked swelling, intolerable pain, and high fever.

Pancreatitis may be another complication of mumps. How often it occurs is impossible to say. The clinical diagnosis is occasionally made on the basis of the appearance of upper abdominal pain, nausea, and vomiting during the course of mumps. Unfortunately, there would appear to be no means of laboratory confirmation, for a study at Camp Adair, Oreg.,[65] showed that the level of blood diastase was elevated in 73 percent of cases of mumps. Only 15 percent of these had any symptoms of pancreatitis, and it was assumed that the diastase originated in the affected salivary glands rather than in the pancreas. In any event, pancreatitis is an unpleasant rather than a serious complication.

The virus of mumps can also cause meningoencephalitis which manifests itself as a rule by headache, some stiffness of the neck, and increased cell count in the spinal fluid. Although more severe central nervous system manifestations can occur, this complication is usually a rather mild one of short duration. Complete recovery is the rule.

In World War I, mumps was third in order of importance as a cause for noneffectiveness; in World War II, with less than half the number of cases, it was obviously less important. However, as the average number of days lost

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[63] Wesselhoeft, C., and Vose, S. N.: Surgical Treatment of Severe Orchitis in Mumps. New England J. Med. 227: 277–280, 20 Aug. 1942.

[64] (1) McGuinness, A. C., and Gall, E. A.: Mumps at Army Camps in 1943. War Med. 5: 95–104, February 1944. (2) Nixon, N., and Lewis, D. B.: Mumps Orchitis; Surgical Treatment. Air Surgeon's Bull. 2: 152–154, May 1945.

[65] Zelman, S.: Blood Diastase Values in Mumps and Mumps Pancreatitis. Am. J.M. Sc. 207: 461–464, April 1944.

to duty for each case was about 18 during World War II, it remained one of the major causes of noneffectiveness among the acute infections, being surpassed only by hepatitis, common respiratory diseases, the pneumonias, gonococcal infections, malaria, syphilis, and dermatophytosis. Mumps usually begins in the late autumn, and there is a slow development of the epidemic during the winter and spring. It is not as explosive as measles. On the other hand, the incidence may rise sharply when a unit with sporadic mumps is closely packed in together for a long period of time, as happens on a transport on a protracted sea voyage.[66]

Experience in the Continental United States

As with other so-called childhood communicables, the greatest incidence of mumps occurs in the first months of Army service. Mumps occurred at some time in all Army camps and, at times, was sufficiently prevalent to be called epidemic. One such epidemic at Camp McCoy, Wis., was reported in detail by McGuinness and Gall. During a 7-month period, 1,378 cases were treated in the station hospital. The slow evolution of the epidemic is noteworthy, the peak of 194 cases not being reached until the 17th week. One group of soldiers was predominantly from the rural areas of the South. This group, roughly equal in size to the other group from the industrialized North, contributed 84 percent of the cases. Nearly half the companies in the northern group had but one case each, whereas in one southern company 19 percent of the men contracted the disease. Orchitis occurred in slightly over 36 percent of the cases in this epidemic as compared to 15 percent of some 250 to 300 cases in an epidemic in two large camps in the Fourth Service Command. This relationship was borne out elsewhere; that is, the larger the epidemic, the higher the incidence of complicating orchitis. Orchidotomies were performed in 83 cases at Camp McCoy with what were described as good results. An attempt to ward off orchitis by enforcing 2 weeks of bed rest was a failure. The complication appeared to be as frequent as in ambulatory patients. Of the entire series of mumps cases, one-third were moderate in degree, and one-third severe. Clinical meningoencephalitis was uncommon.

Other interesting observations were made elsewhere in regard to orchitis. For example, no relationship between incidence of this complication and preceding gonorrhea [67] could be found. Generally speaking, treatment with convalescent serum was found ineffective in preventing orchitis,[68] except in a small series treated with serum drawn from convalescent orchitis cases. Here, there was an apparent reduction in incidence to 4.2 percent from an average of about 20 percent.

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[66] Dermon, H., and Le Hew, E. W.: A Mumps Epidemic in a Small Task Force. Am. J.M. Sc. 208: 240-247, August 1944.

[67] See footnote 66.

[68] Bailey, W. H., and Haerem, A. T.: Some Observations on the Efficacy of Convalescent Serum in Mumps. Mil. Surgeon 90: 134-139, February 1942.

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No advance in treatment of uncomplicated mumps was recorded. At one station hospital in the Third Service Command, atropinizing did not appear to ameliorate symptoms [69] in a small series of cases.

On the whole, it may be stated that, while not infrequently bothersome, mumps did not constitute a very serious military problem.

Experience Overseas

As in measles, mumps was more common in the United States than overseas, although the difference was less marked. About nine times as many cases of measles were reported at home as abroad; about four times as many cases of mumps were reported. This difference is presumably due to the lower communicability of mumps. The disease tended to be mild in the European theater. It was somewhat more common in Negroes than in white troops. A number of complications, particularly orchitis, was observed, but they did not prove very troublesome. It was the writer's impression that bed rest had little influence on the likelihood of development of orchitis.

Routine lumbar punctures were done on a number of consecutive cases of mumps, at the 30th General Hospital,[70] Nottinghamshire, England, and in about half of them the spinal fluids showed pleocytosis. On the other hand, only 10 percent of the cases showed clinical evidence of meningoencephalitis. This indicates that the central nervous system is affected by the virus much more often than was formerly believed but that in most cases the infection is asymptomatic. In this connection, it is worth remarking that a very occasional case of mild encephalitis without mumps was seen in an individual from a unit in which the disease was epidemic. It was suggested that such cases were actually mumps meningoencephalitis without parotitis. This may well be true, although there was, of course, no way of verifying the diagnosis.

The question of length of quarantine of patients was considered by the infectious disease board. The board suggested that isolation of the individual case could be terminated as soon as all evidence of swelling had disappeared and there was no fever or other manifestations. This resulted in considerable shortening of hospital stay for the mild cases and, as far as one could tell, produced no untoward consequences.

From 1 January 1943 to 31 March 1945, inclusive, approximately 1,700 cases of mumps were reported in the Mediterranean theater.

INFECTIOUS MONONUCLEOSIS

Introduction

Infectious mononucleosis is a fairly common disease which affects males somewhat more than females and which shows a predilection for people under

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[69] Potter, H. W., and Bronstein, L. H.: Some Clinical Characteristics of Mumps, and the Effect of Belladonna in Treatment; A Study Made at the Station Hospital, Fort George G. Meade, Maryland. Ann. Int. Med. 21: 469-474, September 1944.

[70] Kirkland, H. B., and Brown, J. W.: Mumps Complicated by Meningo-encephalitis. ETO Med. Bull. 9: 9-10, September 1943.

30 years old. A survey at Harvard University, Cambridge, Mass., in 1944, indicated that it caused 1.5 percent of all student admissions to the infirmary.[71] *Therefore, one would expect to encounter it quite often in the Army.*

It was frequently recognized in the U.S. Army, but it is probable that the reported incidence is considerably below the actual. Infectious mononucleosis presents itself in a number of clinical forms and is often sufficiently vague in character to escape detection unless one is on the alert. The classical form with sore throat, enlargement of the upper deep cervical lymph glands, palpable spleen, and rather prolonged fever, is easily recognized, either immediately or during a workup to exclude such conditions as syphilis or Hodgkin's disease. On the other hand, it is probable that nearly 20 percent of patients have no abnormal lymph gland enlargement. In some cases, the presenting feature is an ulcerative throat infection of the Vincent's type, from which Vincent's organisms are obtained. There may be an associated stomatitis. A small percentage of patients will have jaundice, which may be confused with infective hepatitis of the ordinary type. Some cases show a skin eruption which may be purpuric or resemble German measles. Mumps also may be simulated. Evidence of meningoencephalitis is found on rare occasions. Lastly, some of the cases are extremely mild and therefore likely to be dismissed as undifferentiated respiratory infection.

In connection with jaundice, a study at the Station Hospital, Boca Raton Army Air Field, Fla., is worthy of mention.[72] Serial liver function tests performed in 15 consecutive cases of infectious mononucleosis showed some evidence in every case of deranged liver function, although clinical jaundice was not present in any of the cases. Since World War II, it has become recognized that the cephalin flocculation reaction is almost invariably positive in mononucleosis. It has, in fact, become a useful ancillary aid in diagnosis.

The etiological agent of infectious mononucleosis is still unknown, but is not believed to be any of the several microbes which have been described in the past. It may well be a filterable virus, although transmission experiments have usually been unsuccessful. Nor has the mode of transmission been established. It is apparently infectious, and occasional, localized epidemics with a high incidence have been described. The communicability would seem to be usually rather low as many of the cases are sporadic, without history of contact. Moreover, cases are treated on an open ward in most hospitals, and the disease does not appear to spread under these circumstances. If it is true that infection is widespread but that most of the cases are subclinical, then the phenomenon of apparent low communicability would be explained.

Infectious mononucleosis is a benign disease with a mortality that may be considered nil, though death may result from conditions complicating the

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[71] Contratto, A. W.: Infectious Mononucleosis; A Study of 196 Cases. Arch. Int. Med. 73: 449–459, June 1944.

[72] Cohn, C., and Lidman, B. I.: Hepatitis Without Jaundice in Infectious Mononucleosis. J. Clin. Investigation 25: 145–151, January 1946.

disease, as has been recorded in several reports.[73] The disease may persist for several weeks and require considerable additional time before convalescence is complete. Sixty percent of a series of cases in the Army spent more than 3 weeks in the hospital.

Experience in the Continental United States

During 1944, it became clear that in certain areas in the Fourth and Eighth Service Commands infectious mononucleosis was being more frequently reported than formerly and was presumably mildly epidemic. An extensive clinical study at a station hospital in the Eighth Service Command reviewed the findings in some 556 cases occurring over a period of about a year.[74] Several points of interest were noted in this excellent report. The disease was found in more than the anticipated number of Negroes, in whom it was formerly thought to be rare. Skin manifestations occurred in 16 percent of all the cases, a higher figure than has been commonly recorded. In 23 percent of 223 patients on whom cardiograms were taken, some abnormality was noted, usually of the T-waves. Six percent of the patients were jaundiced, but unequivocal meningoencephalitis occurred only once. The authors also noted 14 cases in which there was radiographic evidence of pneumonitis, a complication which has received scanty attention in the literature. The rest of the clinical manifestations conformed to the varied picture which has already been described. The blood counts were typical, and heterophile antibody titers of 1:112 or higher were noted in most of the cases. Very few had titers below 1:56. False-positive Kahn tests were only noted in 8 of 263 cases, and the incidence of other false serological reactions, that is, Weil-Felix, Widal, cold agglutination, was exceedingly low.

In contrast, what was described as an epidemic of 91 cases of infectious mononucleosis in the Caribbean Defense Command occurred in the autumn of 1944. Of these, 48.7 percent showed an exanthem, and the titer of heterophile antibodies was remarkably low, in the majority being below 1:28. A Weil-Felix reaction of above 1:160 was found in half the cases. Moreover, there were numerous other transient serological reactions, such as the Kahn, Widal, and cold agglutinin tests, a finding which has been noted in typhus. Histological studies of a few excised glands were made at the U.S. Army Medical Museum, Washington, D.C., and the findings were not typical in all of them. Altogether, there is a strong suspicion that this outbreak may have been rickettsial in nature.

In summary, it may be stated that while infectious mononucleosis was fairly common, it was not a serious medical problem in the continental United States. It is estimated from sample tabulations that about 21,000

[73] (1) Bernstein, A.: Infectious Mononucleosis. Medicine 19: 85–159, February 1940. (2) Custer, R. P., and Smith, E. B.: Pathology of Infectious Mononucleosis. Blood 3: 830–857, August 1948.

[74] Wechsler, H. F., Rosenblum, A. H., and Sills, C. T.: Infectious Mononucleosis; Report of an Epidemic in an Army Post. Ann. Int. Med. 25: 113, July; 236, August 1946.

cases occurred in the total U.S. Army during the period 1942–45, of which about 15,000 were in the continental United States.

Experience Overseas

Sporadic cases of infectious mononucleosis were observed in the European theater throughout World War II where the case rate was about one-half that in the United States. At one time, the disease was mildly epidemic in an area of East Anglia, where a considerable number of cases was reported among Army Air Force personnel, and also among the personnel of the 2d Evacuation Hospital. In one of these, a most unusual complication occurred, spontaneous rupture of the spleen. The patient recovered following splenectomy. This epidemic was not of sufficient magnitude significantly to affect military operations.

As might be expected in any disease with such varied manifestations, very unusual clinical cases were observed. One patient, for instance, had a severe thrombocytopenic purpura during the acute phase of the disease.[75] The writer saw a patient who was nearly exsanguinated owing to hemorrhage from an ulcerative pharyngitis. He recovered following transfusions and penicillin therapy. This indicates that the associated Vincent's infection in mononucleosis may be a dangerous complication. No useful purpose is served in multiplying these remembered clinical curiosities.

RUBELLA

Rubella (German measles) is the mildest of the exanthemata of childhood. Unlike the others, it is almost wholly uncomplicated, and the mortality rate is usually stated as nil. The disease is highly communicable, but the symptoms are so trifling and the resulting disability of such short duration that its only importance is its nuisance value. Clinically, it may cause some difficulty in differential diagnosis as it can be mistaken for other diseases, such as measles, infectious mononucleosis, drug eruptions, scarlet fever, or even syphilis.

Although the diagnosis is purely clinical, it seems probable that German measles in its usual form is recognized with some accuracy by clinicians of wide experience. However, the differential diagnosis between it and measles may be difficult for others less experienced. This point is brought up because of certain peculiarities in its reported behavior during World War II. In the first place, unlike measles and mumps, rates were higher than in World War I. This is difficult to explain unless the low rates for the First World War resulted from marked under reporting of a trifling malady. Secondly, seven deaths were ascribed to German measles, and the average days lost to duty (9) was not much lower than the number lost owing to measles (13 days).

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75 Lloyd, P. C.: Acute Thrombocytopenic Purpura in Infectious Mononucleosis; Report of a Case. Am. J.M. Sc. 207: 620–624, May 1944.

Lastly, there was a striking peak in the incidence of German measles in 1943, the year of the highest rate for measles. All these facts create the suspicion that cases of measles were being reported as German measles. The most important differentiating points are the different modes of onset of the two diseases, and the exanthem of true measles.

There were 135,830 cases of German measles reported in World War II, of which 125,530 occurred in the United States. If these figures are accurate, it caused more noneffectiveness than measles. It was an inconsequential malady, of extremely benign character, and presented no clinical features worthy of discussion. However, the interesting observation made in Australia during the Second World War that German measles occurring in the first 2 months of pregnancy is associated with a high incidence of congenital malformations of the newborn [76] was obviously devoid of military significance.

Part II. Chronic Respiratory Diseases

CHRONIC BRONCHITIS

"Chronic bronchitis" is a rather loose diagnostic term which does not usually indicate a clear-cut pathological or, for that matter, clinical entity. One variety is the chronic cough of older men, usually more marked in winter. Some of these individuals may have occasional wheezing rales; in others, there are no noteworthy physical signs. X-rays of the chest may show some exaggeration of the bronchial markings, but often the diagnosis is a presumptive one based on the observation of a chronic cough. As the individual grows older, he may develop varying degrees of emphysema with its attendant effects on respiratory physiology. Cigarette smoking and chronic disorders of the upper respiratory tract are most assuredly contributing factors to the condition. Because of the age distribution of Army personnel, this type of chronic bronchitis was more often seen on the officers wards. In some climates, it tended to get worse. It was the writer's impression, for instance, that elderly officers coughed more in England than they had at home. Dampness, unheated billets, and excessive smoking undoubtedly contributed to this. It has also been remarked that in a tropical climate, such as Panama, soldiers with a history of recurrent acute bronchitis tend to develop chronic bronchitis.[77]

The management of these cases was largely a matter of appraisal. In the author's experience, it was almost always impossible to persuade an officer stationed overseas to stop smoking. If the condition were deemed

[76] Swan, C., Tostevin, A. L., Moore, B., Mayo, H., and Black, G. H. B.: Congenital Defects in Infants Following Infectious Diseases During Pregnancy, With Special Reference to the Relationship Between German Measles and Cataract, Deaf-Mutism, Heart Disease and Microcephaly, and to Period of Pregnancy in Which Occurrence of Rubella is Followed by Congenital Abnormalities. M.J. Australia 2: 201-210, 11 Sept. 1943.

[77] Cohen, A. G.: An Early Form of Chronic Bronchitis in Panama. War Med. 5: 105-108, February 1944.

incompatible with any kind of duty, the patient was boarded home. At times, it was possible to effect a change in his working and living conditions. On the whole, however, there was little in the way of medical treatment which could be offered. Diagnosis of chronic bronchitis was sometimes used as a handy means of returning home elderly officers who had outlived their usefulness in an oversea theater.

A just appraisal of the importance of chronic bronchitis in the Army is difficult. It never seemed to be a major problem, and yet preliminary data based on sample tabulations indicate that the disease was responsible for about 34,000 admissions during the period 1942–45. Nearly half of these occurred overseas. The figure seems extraordinarily high and, perhaps, indicates that the diagnosis was freely used to designate any case of chronic cough.

Mustard gas is a recognized cause of chronic bronchitis. Had this or other irritating inhalants been employed in any of the campaigns, the disease might well have become a major problem. During World War II, virtually the only individuals at risk were those engaged in the manufacture of mustard gas. A few cases were reported.[78]

Asthma.—The dividing line between chronic bronchitis and asthma is often not very clear cut. In younger individuals, chronic bronchitis is often of an asthmatic character; that is, it may be really a manifestation of asthma of the endogenous or intrinsic type. These asthmatic bronchitides tended to get worse overseas.[79] Moreover, it is interesting to note that, in one series of 28 asthmatics whose initial attack occurred in the Army, in 23 it developed overseas.[80] This is presumably related to heavy pollination in certain tropical areas. At the same time, intrinsic asthma was aggravated during the tropical rainy season.

The management of asthma in the Army is fraught with discouragement. In civilian practice, one can perform an exhaustive study and, depending upon the findings, endeavor to modify the external environment or to exert influence on the patient, by either improving his respiratory disease status or actually rendering him less sensitive. None of these is feasible during a military campaign, save in very exceptional instances. The clinical management of asthma, apart from symptomatic treatment, consists principally in appraisal. By observing the patient over a considerable period of time, the medical officer tries to answer the following questions: Is this man capable of full duty? Of limited duty? Should he be boarded home from an oversea theater or, if at home, separated from the service?

Most medical officers believed that very few asthmatics, no matter how mild their disease, were fit for combat duty. Exertion and dust, for in-

[78] Morgenstern, P., Koss, F. R., and Alexander, W. W.: Residual Mustard Gas Bronchitis; Effects of Prolonged Exposure to Low Concentrations of Mustard Gas. Ann. Int. Med. 26: 27-40, January 1947.

[79] See footnote 19, p. 9.

[80] Alford, R. I.: Disposition of Soldiers With Bronchial Asthma. J. Allergy 15: 196-202, May 1944.

stance, tended to produce some shortness of breath in these individuals even when the asthma did not seem to be clinically active. On the other hand, many such individuals could be retained on a limited duty status either overseas or at home. It must be added, however, that this was partly dependent on the man's willingness to serve. Asthma undoubtedly has a psychosomatic aspect, and if a relatively mild asthmatic wished to get himself sent home from an oversea theater, he usually succeeded in doing so. Mild asthma often got worse overseas. Thus, asthma was one of the leading medical causes for return to the Zone of Interior. The disposition of asthmatics in the United States may be indicated by a report of 100 consecutive patients, of whom 71 were discharged from the service.

BRONCHIECTASIS

In young individuals, bronchiectasis may be a progressive and disabling disease. The likelihood of such a person being accepted for military service is extremely remote, and it has been stated that bronchiectasis was the most common form of chronic nontuberculous lung disease discovered on induction examination. However, bronchiectasis of a milder type, essentially cylindrical rather than saccular, may be discovered in a soldier who has previously been in reasonably good health. The pathogenesis of the condition is somewhat obscure, but the lesions may arise apparently as a result of sinusitis, following pneumonia, or in older individuals as a consequence of chronic bronchitis. Bronchiectasis by itself does not necessarily produce any physical signs or X-ray changes. It is likely, therefore, that the disease is overlooked on occasion. Undoubtedly, if more bronchographic studies were performed, it would be more frequently recognized.

Bronchiectasis has been termed the most common chronic pulmonary disease in the U.S. Army.[81] As evidence of this, the authors reported 95 cases investigated bronchographically, mostly for slowly resolving pneumonia. Of these, 37 showed frank and 24 minimal bronchiectasis. No bronchiectasis was found in 34 patients. Two other reports might be cited, both from station hospitals in the Third Service Command: At Fort Belvoir, Va., 33 cases were discovered during the course of a year[82]—14 were said to be severe, 9 moderate, and 10 minimal. At Fort Eustis, Va., the diagnosis was made 40 times over a 15-month period;[83] 9 patients were studied because of chronic cough, and the rest were admitted with a diagnosis of atypical pneumonia. When resolution failed to occur in 4 to 6 weeks, bronchographic studies revealed the true condition. Only 23 of the entire series

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[81] Evans, W. A., Jr., and Galinsky, L. J.: The Diagnosis of Bronchiectasis in Young Adults; Prebronchographic Roentgen Manifestations Observed Among Military Personnel. Am. J. Roentgenol. 51: 537-547, May 1944.

[82] Thompson, T. E., Jr., Cawley, F. C., and Seltzer, A.: A Study of Bronchiectasis at Station Hospital, Fort Belvoir, Virginia. M. Ann. District of Columbia 13: 93-97, March 1944.

[83] Grier, G. S., III: Importance of Bronchography in Cases of Unresolved Pneumonia. Arch. Int. Med. 73: 444-448, June 1944.

gave a long history of chronic cough. These patients did not show the typical textbook picture of severe bronchiectasis with wasting, foul sputum, clubbed fingers, and so forth. The disease was obviously in a much milder, or earlier, stage. The author of this study did not believe that these slowly resolving pneumonias were primary atypical pneumonia but rather that they were of the variety long recognized as occurring in conjunction with symptomatic flareups of bronchiectasis. Some internists believe that chronic bronchiectasis is at times a rare sequel of severe atypical pneumonia. For instance, the disease was believed to follow atypical pneumonia in no less than 17 of 33 cases admitted during a 9-month period to the Percy Jones General Hospital, Battle Creek, Mich.[84] However, a review of the case reports given in this paper leaves serious doubts as to the diagnosis of atypical pneumonia. Flareups of pneumonitis are a common feature of bronchiectasis, and the differentiation of these from primary atypical pneumonia is extremely difficult. Van Ravenswaay and his associates[85] stated that bronchiectasis occurred as a sequel to atypical pneumonia at Jefferson Barracks in 11 of 1,862 cases. This question is not yet entirely settled. On the other hand, dilated bronchi, which later reverted to normal, have been shown in a few patients convalescing from atypical pneumonia.[86] The condition was termed "pseudobronchiectasis."

It is estimated that the disease caused more than 6,000 admissions in the period 1942–45, four-fifths of them in the continental United States. When the diagnosis was established, it was ordinarily a cause for separation from the service.

A certain number of cases were treated surgically during World War II. For example, in 1943, 25 lobectomies were performed at Fitzsimons General Hospital, Denver, Colo., with 2 deaths.

LUNG ABSCESS

The possibility that a person with a chronic lung abscess could pass the induction X-ray and physical examination is so slight that cases of this condition observed in the U.S. Army presumably developed in the service. Acute lung abscess is by no means uncommon in civilian practice; such cases follow a fairly well recognized clinical pattern, and a considerable percentage, perhaps nearly half, recover spontaneously without surgical drainage. The remainder will become chronic if not drained. Acute abscesses of this type coming on de novo, so to speak (in the absence of such predisposing factors as dental extraction and tonsillectomy) were very rarely encountered in the Army. The reason for this is not entirely clear unless it be the generally low incidence of bacterial pneumonias. Lung abscess

[84] Kay, E. B.: Bronchiectasis Following Atypical Pneumonia. Arch. Int. Med. 75: 89–104, February 1945.

[85] see *footnote* 46, p. 20.

[86] Blades, B., and Dugan, D. J.: Pseudo Bronchiectasis Following Atypical Pneumonia. Bull. U.S. Army M. Dept. No. 70, pp. 60-68, November 1943.

developing after surgical procedures also seemed unexpectedly rare. It is the writer's impression that many of the lung abscesses seen in the Army were in battle casualties.

The disease is estimated to have been responsible for about 500 admissions in the 1942–45 period, with 16 deaths.

SPONTANEOUS PNEUMOTHORAX

The sudden appearance of air in the pleural cavity not due to penetrating wounds of the chest wall or endotracheal [illegible] is known as spontaneous pneumothorax. It was formerly the [illegible] related to tuberculosis. Now, however, while it is known that spontaneous pneumothorax may occasionally occur as a complication of frank pulmonary tuberculosis, it is also recognized that the great majority of cases take place as a result of rupture of a subpleural bleb and have no relationship with tuberculosis whatsoever. Interestingly enough, rupture often takes place quite independently of physical exertion.

In many instances, pneumothorax is a recurrent disease. Recurrences were formerly thought to be uncommon, but it now seems likely that if more frequently recognized by general practitioners their incidence would rise. For example, a report from the Station Hospital, Seymour Johnson Field, Goldsboro, N.C.,[87] points to a highly suggestive history of one or more previous episodes in five out of seven carefully studied cases.

Spontaneous pneumothorax is most frequently encountered in relatively young males and gives rise to characteristic physical signs only if the amount of escaped air is large enough. Roentgen examination, however, as a rule is unequivocal; and if chest X-rays are routinely taken of individuals giving a suggestive clinical history (there is almost invariably some sudden chest pain at the onset followed by varying degrees of dyspnea), the condition should not be overlooked. Pneumothorax is rarely complete; in probably three-fourths of the cases, the collapse is less than 50 percent, so that the number of cases not detectable with assurance on physical examination is high. Following spontaneous pneumothorax, fluid may occasionally appear, but these effusions are small.

In the usual course of events, there is a single leakage of air which will be absorbed in the course of time. On the other hand, there may be recurrent leakages during the reexpansion period, or the pneumothorax may be permanent due to an open fistula. Such cases require the attention of the thoracic surgeon. Another clinical variety is the so-called tension pneumothorax wherein so much air escapes (often aided by a valve effect in the rent pleura) that dangerously high intrathoracic pressures are produced. Fortunately, this is a rare happening, but when it occurs, it may constitute a real medical emergency. The patient is extremely dyspneic and cyanotic,

[87] Pease, P. P., Steuer, L. G., and Chapman, A.: Spontaneous Pneumothorax in Soldiers. Bull. U.S. Army M. Dept. No. 82, pp. 102-107, November 1944.

and his gasping respirations only serve to aggravate the situation. In such instances, the quick release of air by means of a needle plunged through the chest wall is lifesaving. Lastly, the rare phenomenon of hemopneumothorax might be mentioned. Here, bleeding occurs from the torn pleura, sometimes on a large scale.

There were 3,831 admissions for spontaneous pneumothorax to U.S. Army hospitals between 1942 and 1945. It was about twice as common at home as overseas. The vast majority of these cases were of the uncomplicated benign type, and in about 10 percent was the condition a cause for separation from military service. Recurrence was the reason for most of the discharges. The average duration of hospitalization was in the neighborhood of 2 months, so that neither in terms of man-days lost nor manpower permanently lost did the disease constitute a serious medicomilitary problem. The four deaths attributed to the condition were presumably due to tension pneumothorax.

In 1944, at the suggestion of the National Research Council, a booklet on spontaneous pneumothorax was prepared for general distribution by Dr. James J. Waring.[88] In this, he advocated conservative therapy, with emphasis on hospitalization, bed rest, and the avoidance of air transport. Dr. Waring also discussed the indications for thoracotomy, chemical pleuritis in the recurrent cases, and the disadvantages of these procedures. In general, he advised an individualized approach to each case.

PULMONARY FIBROSIS

Diffuse fibrosis of the lungs may follow granulomatous diseases, such as tuberculosis, fungus infections, sarcoidosis, and beryllium poisoning. It is also a serious occupational hazard of those exposed to the inhalation of silica dust. The preinduction X-ray screening of U.S. Army personnel in World War II made it highly improbable that individuals with any significant degree of pulmonary fibrosis would be accepted for military service. Moreover, the conditions leading to its development were not a feature of army life, so that, apart from a certain amount secondary to chronic pulmonary tuberculosis, it was never a feature of medicomilitary practice. It might be added that the only generalized fungus infection with a fairly high incidence in the Army, coccidioidomycosis, is not a recognized cause of diffuse pulmonary fibrosis.

Peculiar instances of rapidly progressive pulmonary fibrosis whose etiology is entirely obscure have been recorded in the literature. Notable among these is the report of Hamman and Rich.[89] It is of interest that four

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[88] Waring, J. J.: Spontaneous Pneumothorax. Office of Medical Information, Division of Medical Sciences, National Research Council, July 1944.

[89] (1) Hamman, L., and Rich, A. R.: Acute Diffuse Interstitial Fibrosis of the Lungs. Bull. Johns Hopkins Hosp. 74: 177-212, March 1944. (2) Eder, H., Hawn, C. V., and Thorn, G. W.: Report of a Case of Acute Interstitial Fibrosis of the Lungs. Bull. Johns Hopkins Hosp. 76: 163-171, April 1945.

cases thought to resemble those described by Hamman and Rich were observed in the U.S. Army in New Guinea in 1944. Of these, one patient finally recovered while two were evacuated and lost to followup study. One came to autopsy.

PULMONARY EMPHYSEMA

Chronic pulmonary emphysema was occasionally noted in the U.S. Army in the older age groups, particularly among officers. It was less common than in civilian practice, probably owing to the generally higher standards of health prevailing in the Army. It was said to be responsible for about 750 admissions in the period of 1942–45, most of them in the continental United States.

MALIGNANT DISEASE OF THE LUNGS

The incidence of malignant disease generally in the U.S. Army is very low, owing to the age group involved. Moreover, a survey of 15 million Army man-years in the 20- to 40-year age group made in 1944–45 indicated that the incidence in this group was lower than among civilians.[90] The reason for this difference is not apparent. In any case, cancer occurs with expected frequency in the older age group, again particularly among officers.

As a measure of the importance of malignant disease of the lungs in military medicine, the following is cited: Bronchogenic carcinoma is estimated to have been recognized 200 times during the period 1942–45. There were 91 cases of all forms of malignant diseases of the lungs identified at Letterman General Hospital, San Francisco, Calif., between 1944 and 1950. This represented almost exactly 1 per 1,000 admissions.[91]

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[90] Lindsey, D., and Cohart, E. M.: Incidence of Cancer in American Males; 15,000,000 Man-Years of Aggregate Experience, United States Army, 1944–45. Cancer 3: 945–959, November 1950.

[91] For the surgical aspects of diseases of the chest see Bades, Brian B., Carter, B. Noland, and DeBakey, Michael E.: Surgical Aspects of Diseases of the Chest. *In* Medical Department, United States Army. Surgery in World War II. Thoracic Surgery. Volume II, ch. XI. [In preparation.]—J. B. C., Jr.

CHAPTER II

Sandfly Fever

William A. Reilly, M.D., Roberto F. Escamilla, M.D., and Perrin H. Long, M.D.

The diagnosis of sandfly fever was not made as frequently as it should have been, because of an unfamiliarity with the disease and a certain reluctance on the part of medical officers to make the diagnosis solely from the clinical picture.[1]

Sandfly fever, also known as Phlebotomus fever and pappataci fever, attained importance in Allied and Axis forces in the Mediterranean (formerly North African) Theater of Operations, U.S. Army, in World War II by incapacitating large numbers of men for periods of 7 to 14 days, or longer. This disease was known to be endemic in the Mediterranean littoral and was first recognized in U.S. forces in North Africa toward the end of April 1943. Although not reported as such in the statistical health report (WD MD Form 86ab), the first patients were seen at the 77th Evacuation Hospital then situated near Bône, Algeria. At that time, typical cases were described, and a careful study was made of the relation and importance of meningeal irritation to the general findings in the disease. The patients had come from the U.S. II Corps which was then engaged against the enemy in northern Tunisia. At the same time that these patients were being studied and the disease recognized in the 77th Evacuation Hospital, an increased incidence of influenza was observed by the medical services of the other evacuation hospitals within the corps area and also a sharp increase in the number of cases of F.U.O. (fever of undetermined origin) was noted in the statistical health report for April 1943. While no careful search for sandflies was conducted by trained entomologists during that period, it is known that sandflies, *Phlebotomus papatasii*, were captured and identified as such in northern Tunisia by certain British medical officers and by members of the hygiene section of the British First Army.

While knowledge concerning the incidence of sandfly fever in U.S. forces in North Africa during the summer of 1943 is obscured by the fact that the diagnosis was infrequently made and doubtlessly most of the cases were classified as F.U.O., the disease is known to have occurred frequently in the region of Tunis, Mateur, Ferryville, and Bizerte in Tunisia; also

[1] Letter, Lt. Col. Perrin H. Long, MC, Consulting Physician, Office of the Surgeon, Headquarters, NATOUSA, to the Surgeon, NATOUSA, 24 Aug. 1943, subject: A Report Upon Medical Services in Sicily.

around Oran and Algiers in Algeria.[2] Cases of the endemic disease were noted in members of the Allied forces in Algiers and, in at least one instance, a fairly extensive outbreak occurred among members of a signal corps detachment which was situated just outside the city. In this outbreak, the disease was thought to be dengue until a review of the clinical findings in the disease revealed the absence of secondary rises in fever. An entomological survey of the area of this detachment established the presence of many sandflies of the variety *P. papatasii.*

A review of the plans for the amphibious operation in Sicily which dealt with the professional services shows that sandfly fever was considered a likely threat to manpower during the Battle of Sicily and that the peak of the disease would be reached after 1 August 1943. This prediction was more than realized, because the disease which had been contracted in North Africa began to make its appearance on D-day in Sicily, and, while no cases of the disease were reported in the statistical health report for NATOUSA (North African Theater of Operations, U.S. Army) for July 1943, in reality, there were hundreds of cases of sandfly fever in the troops in Sicily during that month. This lack of reporting was due to the diffidence that medical officers then showed in making the diagnosis of the disease from the clinical findings alone.[3]

Despite the reporting of but 104 cases, the disease reached epidemic proportions in Sicily because it was a favorable summer for the propagation of sandflies, the type of fighting was from village to village, native habitations were used as billets, and discipline in respect to the use of nets and insect repellents was poor. Sampling studies made in division clearing companies and evacuation hospitals during the first 2 weeks in August produced clinical evidence that, at a minimum, at least 25 percent of the cases diagnosed as F.U.O. should have been diagnosed as sandfly fever. During the latter half of the month of August and the first half of September, this same percentage probably prevailed.

The invasion of Italy by way of the beaches at Salerno (an area in which sandflies were common) was attended by a large number of cases of sandfly fever. This invasion was spearheaded by the 36th Infantry Divi-

[2] In May 1943, shortly after Von Armin's army was driven out of Tunis, contact was possible with U.S. Army Forces in the Middle East (Egypt) and the Persian Gulf Service Command (Iran-Iraq). Reports of the extensive outbreaks of sandfly fever there, which occurred in U.S. personnel, were beginning to be available although it was apparent that in these areas, too, medical officers were loath to make the diagnosis, preferring F.U.O. or influenza.

[3] An analysis of the possible extent of sandfly fever cases in the Sicilian campaign, nearly all of which were probably erroneously diagnosed as malaria or conservatively labeled F.U.O., was the subject of a special report made by Maj. (later Lt. Col.) Albert B. Sabin, MC, in September 1943. This report was subsequently published in part by Major Sabin, Lt. Col. Cornelius B. Philip, MC, and Dr. John R. Paul. The conclusion reached by Major Sabin was that sandfly fever was probably responsible for as many, if not more, cases of fever as malaria. (1. Letter, Maj. Albert B. Sabin, MC, to Chief Surgeon, Seventh Army: Col. Daniel Franklin, 7 Sept. 1943, subject: Estimate of Extent to Which Sandfly Fever Was and Is a Problem Among American Forces in Sicily. 2. Sabin, A. B., Philip, C. B., and Paul, J. R.: Phlebotomus (Pappataci or Sandfly) Fever: A Disease of Military Importance: Summary of Existing Knowledge and Preliminary Report of Original Investigations. J.A.M.A. 125: 603 606, 1 July 1944.)

sion, a unit which had had little experience with sandfly fever and hence was comprised mainly of susceptible persons. Again, as in Sicily, the troops made use of buildings both as strong points during the fighting and subsequently as billets, and discipline in the use of nets and repellents was poor. Because of certain command difficulties, it was impossible to have an adequate study made of the F.U.O. cases in Fifth U.S. Army hospitals during September and early October, so that an approximation of the number of cases of sandfly fever was not made, although from the rather meager data at hand it seemed probable that the incidence of the disease in the Fifth U.S. Army during this period was similar to that experienced by the Seventh U.S. Army in Sicily.

In 1944, in Italy, the situation in respect to the diagnosis of sandfly fever was considerably improved, and the figures for that year were much more representative of the actual incidence of the disease than they were in 1943. However, it must be recorded that, even after an indoctrination campaign had been conducted in the diagnosis of sandfly fever, there were many medical officers who, because a specific diagnostic test for this disease did not exist, preferred to make the diagnosis of F.U.O. Frequent examples of this failure to make the proper diagnosis were encountered in the monthly essential technical medical data reports, in which medical officers, after having described classical examples of the disease, would state that although sandflies are known to exist in this area, the fact that none of the patients had seen the insects and few if any gave a history of having been bitten by sandflies, the diagnosis of sandfly fever could not be definitely established and that, hence, the cases were classified as being F.U.O.

In MTOUSA (Mediterranean Theater of Operations, U.S. Army), during the winter of 1944 and spring of 1945, an intensive campaign of education was carried out in respect to the clinical findings in sandfly fever. The effect of this campaign became evident because the incidence of sandfly fever as reported in the statistical health reports for May, June, and July, 1945, reflected the true incidence of the disease.

While the literature upon disease in the Wehrmacht was scanty, it was known that German troops based in the Mediterranean area suffered from sandfly fever. Hallmann,[4] in 1941, described an outbreak of sandfly fever that occurred in German soldiers who were stationed in the islands and the Greek mainland near Athens. The majority of the cases of the disease were seen in July and August, and it was estimated that 20 percent of all the troops in the area had the disease during this time. In a report printed in Berlin in 1944,[5] an analysis of 5,890,000 records for admissions to hospitals for sickness in the German Army from 1 September 1939 to 31 March 1943 was made. Of the admissions recorded in this report, 1,062,920 were for

[4] Hallman: Beitrag zum Pappatacifieber 1941 auf der Balkanhalbinsel. Deut. trop. Ztschr. 43: 64–68, 1 Feb. 1943.

[5] Die Infektionskrankheiten im jetzigen Kriege. Anlage zu Der Heeres-Sanitätsinspekteur. Nr. 8715/44 geh. (Wi G) Prüf Nr. 50. Berlin, den 28.8.1944.

infectious diseases. Sandfly fever (Pappatacifieber) was 13th on the list as a cause for admission with 4,941 cases recorded without any deaths and with an average period of hospitalization of 13.4 days. Inasmuch as the Wehrmacht had a large number of troops stationed in the Mediterranean and Black Sea littorals in 1941, 1942, and 1943, it is astounding that but 4,941 cases of sandfly fever were recorded. It is especially surprising when one considers that in this study no mention was made of the existence of F.U.O. The truth of the matter probably lies in the fact that during this same period a total of 159,890 cases of "grippe" were recorded from hospital reports. It is likely that many cases of sandfly fever were reported incorrectly under this diagnosis.

ETIOLOGY

It was established in 1908 by Doerr, Franz, and Taussig [6] that the causative agent of sandfly fever is a filterable virus and that the midge, *P. papatasii*, is the vector of this disease. This finding was confirmed by other observers [7] and also by Sabin, Philip, and Paul. Sabin and Paul studied the disease in Sicily after the end of the Sicilian campaign in 1943. As a result of their studies, they obtained the following information regarding the virus of sandfly fever:

> Virus is present in the blood of patients 24 hours before the onset of fever and during the first 24 hours thereafter; it is no longer demonstrable 48 hours after onset. It may be passed serially in volunteers by parenteral inoculation although the intracutaneous and intravenous routes were more effective than the intramuscular or subcutaneous routes. Attempts to recover virus from the spinal fluid obtained in the first 2 days of the experimentally produced disease were unsuccessful. The virus survived in the frozen state at Dry Ice box temperature or in the lyophilized state in an ordinary refrigerator for 6 months. The size of the virus as determined by filtration through gradocol membranes appeared to be not larger than 25 to 37 mμ, although the low titer of virus (1,000 minimum infectious doses per ml. of serum) suggests the possibility that it might be even smaller. Unsuccessful attempts were made to inject embryonated eggs and a wide variety of species including young baboons (*Papio hamadryas*) and monkeys of the following species: grivet (*Cercopithecus griseoviridis*), vervet (*Cercopithecus aethiops pygerythrus*), red African hussar (*Cercopithecus [Erythrocebus] patas*), *Macaca radiata* and *Macaca mulatta* (*rhesus*). The rodents included young white mice, wild gray mice, Syrian hamsters, Egyptian desert rats (jerboas), rabbits, guinea pigs, and cotton rats.

As cited by Warren and Johnson,[8] Sabin also showed that there was more than one strain of sandfly fever virus. Volunteers who had been inoculated

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[6] Doerr, R., Franz, K., and Taussig, S.: Das Pappatacifieber. Leipzig und Wien: Franz Deuticke, 1909.

[7] (1) Birt, C.: Phlebotomus Fever in Malta and Crete. J. Roy. Army M. Corps 14: 236–258, 1910. (2) Birt, C.: Sand-fly Fever in India. J. Roy. Army M. Corps 15: 140–147, 1910. (3) Tedeschi, A., and Napolitani, M.: Experimentelle Untersuchungen über die Aetiologie des Sommerfiebers. Centralbl. F. Bakteriol. 57: 208–211, 1911. (4) Shortt, H. E., Poole, L. T., and Stephens, E. D.: Sandfly Fever on the Indian Frontier; A Preliminary Note on Some Laboratory Investigations. J. Roy. Army M. Corps 63: 361, December 1934; and 64: 17, January 1935. (5) Shortt, H. E., Poole, L. T., and Stephens, E. D.: Note on Some Experiments With Sandfly Fever Blood and Serum. Indian J.M. Research 23: 279–284, July 1935. (6) Moshkovsky, Sh. D.: Studies on Pappataci-Fever. Med. Parasitol. and Parasitic Dis. Moscow 5 (No. 6): 823–862, 1936.

[8] Warren, R. O. Y., and Johnson, J. W., Jr.: Sandfly Fever in NATOUSA. M. Bull. Mediterranean Theat. Op. 3: 160–164, May 1945.

with a strain of virus obtained from a patient in the first day of his illness in Caserta, Italy, developed typical sandfly fever; they were not subsequently protected by this attack against an inoculation with the Sicilian strain of the virus.

EPIDEMIOLOGY

It is believed that *P. papatasii* is the chief vector of sandfly fever in NATOUSA. The adjacent shores and islands of the Mediterranean, Adriatic, and Aegean Seas which were included in the North African and Mediterranean theaters have long been known as favorable breeding places for the moth midges of the genus *Phlebotomus*. The hilly and rocky terrains of Algeria, Tunisia, Sicily, Sardinia, Corsica, and Italy and the adobe or stone houses which dot these areas give rise to what was aptly called "the classical sandfly situation," by Maj. Marshall Hertig, SnC. The female sandfly by choice seeks rocky places, cracks in masonry, buildings, stone walls, or rubble and caves in which to lay its eggs; the adult midges seek outdoor shelter in caves, cracks in stones and buildings, and under the eaves of buildings. A cool, shaded, slightly damp environment is ideal for the life of this insect.

Sandflies rest during the day and feed during the night. The female alone bites, an act which she performs persistently and viciously; a meal of blood is necessary for proper ovulation (fig. 1).

The incidence curves of sandfly fever and F.U.O. in NATOUSA-MTOUSA from January 1943 to December 1945 are presented in chart 1. The first cases of sandfly fever were reported in August 1943 although the disease was recognized in North Africa as early as April 1943. In 1943, the peak monthly rate (September) was 7.9 per 1,000 per annum, a rate doubtlessly far below the actual rate, because the vast majority of cases of sandfly fever were reported as F.U.O. Since careful studies were not made upon any sample group of cases of F.U.O. in 1943, there was little information about the correct diagnoses at the time of the final disposition of these patients, and it will never be known what percentage of patients diagnosed as having F.U.O. during the summer of 1943 were in reality suffering from sandfly fever. It is to be remembered, however, at this point, that many cases of malaria were also classed as F.U.O. in 1943 and that the total rate does not primarily represent undiagnosed cases of sandfly fever.

The incidence curve during 1944 more closely approximated the true incidence, since medical officers were beginning to have some familiarity with the disease and hence were more prone to make the correct diagnosis. In an interesting study of F.U.O.[9] made by Maj. Emil C. Beyer, MC, it was found that a diagnosis of sandfly fever was made at the final disposition in 2.4 percent of 450 cases initially undiagnosed upon admission as F.U.O. during the months of June, July, and August, 1944. However, in this same group,

[9] Beyer, E. C.: Fever of Undetermined Origin. M. Bull. Mediterranean Theat. Op. 3: 208-209, June 1945.

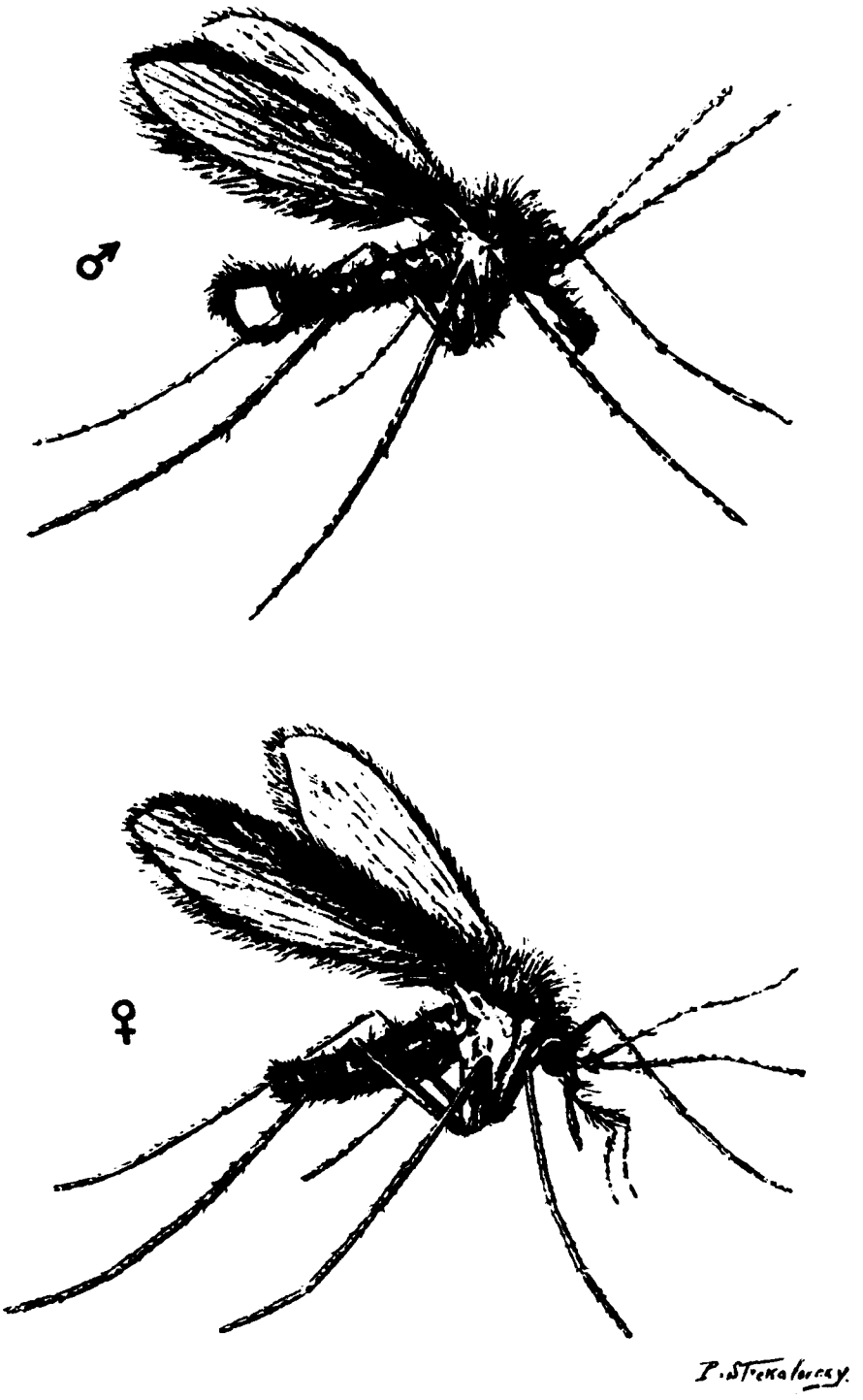
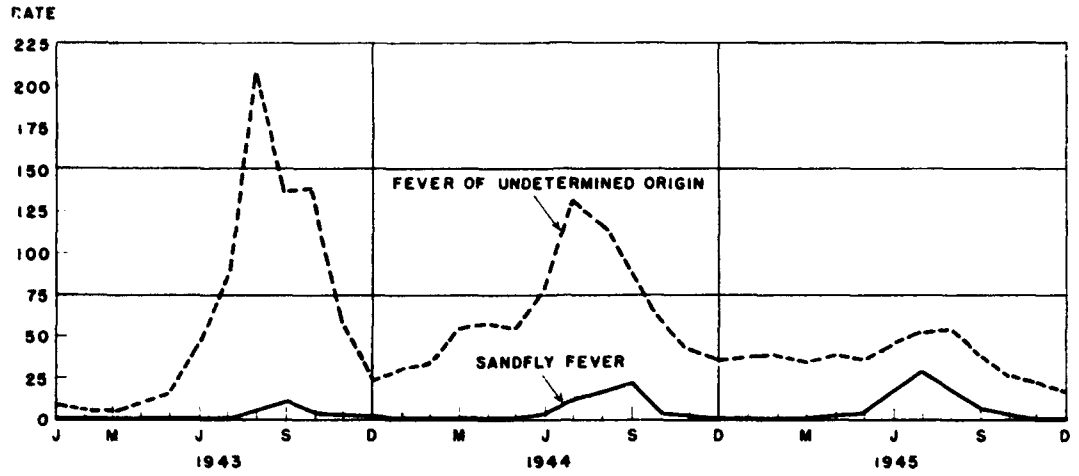


FIGURE 1.—Male and female of *Phlebotomus papatasii*, the vector of sandfly fever. (Sabin, Philip, and Paul. J.A.M.A. 125: 603–606, 1 July 1944.)

CHART 1.—*Incidence of sandfly fever and fever of undetermined origin in the North African-Mediterranean Theater of Operations, U.S. Army,*[1] *1943–45*

[Preliminary data based on summaries of statistical health reports]
[Rate expressed as number of cases per annum per 1,000 average strength]



[1] The North African Theater of Operations was redesignated the Mediterranean Theater of Operations on 1 November 1944.

the diagnosis of F.U.O. or of febricula appeared in 8.4 and 10.7 percent, respectively, of the final dispositions made during that period. Thus, the etiology of 19.1 percent of the patients having fever was in doubt at the time of their final disposition, and it is possible that many of those patients may have had sandfly fever. That this is probable is evidenced by a further study of the diagnoses which were recorded at the time of the final disposition of a similar group of patients, which was made by Major Beyer during January 1945. In this group only 8.9 percent were discharged with a final diagnosis of febricula or F.U.O. It is unknown how many times the original diagnosis of F.U.O. was changed to sandfly fever in the statistical health reports, but on the basis of these figures, there is a possibility that about 10 percent of the patients originally diagnosed as having F.U.O. in the summer and early fall of 1944 had sandfly fever.

The incidence curve of sandfly fever for 1945 probably represented the incidence of this disease quite accurately as the rates for F.U.O. were at low levels in comparison with corresponding months in 1943 and 1944.

As will be noted from chart 1, cases of sandfly fever made their initial appearance in NATOUSA-MTOUSA in April and gradually built up to a peak in September; following this, there was a rapid decline within the next 2 months. Thus, the epidemiological pattern of the disease reflected accurately the life cycle of *P. papatasii.*

IMMUNITY

A natural resistance to sandfly fever apparently does not exist, and a large percentage of susceptibles develop the disease if left unprotected in an

endemic area. Livschitz[10] reported that practically 100 percent of experimentally inoculated volunteers who had had no previous contact with the disease were found to be susceptible, while Sabin, Philip, and Paul stated that approximately 95 percent of their volunteers contracted the disease following their inoculation with virus. This same high rate of susceptibility was observed in U.S. forces when they were introduced into NATOUSA-MTOUSA, and instances were recorded in which 80 percent of a command contracted the disease in certain areas around Caserta. These observations were similar to those made by Cullinan and Whittaker[11] in the Middle East, where rates for sandfly fever of approximately 1,000 per 1,000 per annum or more were recorded in other ranks in two British general hospitals which had been located in areas in which sandflies were abundant and in which sandfly fever was epidemic.

It was recognized also that second, third, or even more attacks of sandfly fever could occur in the same individual and even the same epidemic season. Livschitz observed that the initial rate of attack of the natural infections in a group of 1,076 persons, who were newcomers in an endemic area, was about 50 percent and that 22.8 percent and 0.9 percent, respectively, of 416 persons who had recovered from an initial infection had second and third attacks of the disease within the same epidemic season. Cullinan and Whittaker reported that 15 percent of the noncommissioned officers and other ranks in two British general hospitals had second attacks (and some even third attacks) of sandfly fever during a period of 3 months in which these men were exposed to the disease in an epidemic area.

While there can be little doubt that an immunity to sandfly fever generally results from an attack of the disease, the observations which have just been recorded suggest that at times the immunity may not be solid. However, Sabin's investigations,[12] previously mentioned, indicated the existence of at least two different strains of virus and suggested the possibility that second attacks within the same epidemic season or later may have been the result of an infection with a different strain of virus rather than waning immunity from the first attack.

CLINICAL COURSE AND DIAGNOSIS

Sandfly fever in NATOUSA-MTOUSA was characterized by the sudden onset of fever, headache and severe retro-orbital pain, photophobia, generalized aching, malaise, and chilly and feverish sensations. Anorexia, nausea, and vomiting occurred in some patients. The face was suffused, the conjunctivas and scleras injected, and not infrequently pressure over the eyeballs caused pain. At times, a very faint pink erythema was present over

[10] Livschitz, J. M.: Studies on Pappataci Fever. Med. Parasitol. and Parasitic Dis. Moscow 6 (No. 6): 938-943, 1937.

[11] Cullinan, E. R., and Whittaker, S. R. F.: Outbreak of Sandfly Fever in Two General Hospitals in the Middle East. Brit. M.J. 2: 543-545, 30 Oct. 1943.

[12] See footnote 8, p. 52.

the shoulders and thorax, and the spleen was palpable in a small percentage of patients. Many of the patients had relative bradycardia. The fever lasted from 1 to 11 days, averaging 4 days, and was followed by a variable period of asthenia. In one large group of patients, the period of hospitalization ranged from 1 to 25 days, averaging 6.2 days. Leukopenia was present in most cases at the time the patients entered the hospital with the lowest counts being recorded in the immediate postfebrile period. The differential count was characterized by a relative or absolute increase in the lymphocytes (often with the appearance of large atypical forms) and an absolute increase in many patients in the younger types of the polymorphonuclear cells.

It is not unusual that the disease caused diagnostic difficulties in medical installations in MTOUSA. In its milder aspects, it simulated the milder forms of influenza. At times, the onset was similar to that of malaria, infectious hepatitis, or primary atypical pneumonia, and it required much aid from the laboratory to differentiate promptly and accurately between these diseases and sandfly fever.

On occasion, the occurrence of nuchal rigidity in patients with signs and symptoms characteristic of sandfly fever made the differential diagnosis bebetween this disease of aseptic meningitis difficult.[13] Because of the lack of specific serological tests, the diagnosis of sandfly fever could not be made in patients with evidence of meningeal irritation and pleocytosis of the spinal fluid, and it could not be proved that sandfly fever virus caused the aseptic meningitis syndrome. In experiments with volunteers, Sabin, Philip, and Paul did not believe that it occurred in any of 150 volunteers.

It is evident that, at times, the diagnosis of sandfly fever was difficult and that it required much clinical acumen and confirmation by the laboratory. However, too often in MTOUSA, the reluctance to make the diagnosis resulted from intellectual slovenliness and from the ease with which, for diagnostic purposes, the disease could be classified as F.U.O.

TREATMENT AND PREVENTION

The treatment of sandfly fever in NATOUSA-MTOUSA was purely symptomatic in type.

It was found in NATOUSA-MTOUSA that the prevention of sandfly fever was dependent upon the precautions taken by the individual against being bitten by sandflies and upon environmental control measures aimed at the eradication of sandflies.

SUMMARY

Sandfly fever was a problem of great importance to the U.S. Army in NATOUSA-MTOUSA, and it was responsible for much loss of manpower during the summers of 1943 and 1944.

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[13] See footnote 8, p. 52.

Due to the variations in the clinical picture of sandfly fever, and because specific tests for establishing its identity were not available, medical officers were often reluctant to make the diagnosis of this disease on the basis of their clinical findings. As a result, many thousands of cases of sandfly fever were probably recorded as F.U.O., and hence, the data recorded in the statistical health reports from NATOUSA-MTOUSA regarding this disease were inaccurate.

Sandfly fever could have been prevented in the areas in which the disease was endemic if the proper individual precautions for the prevention of this disease had been observed and if a program for the environmental control of sandflies based upon the use of DDT (dichlorodiphenyltrichloroethane) sprays had been instituted.

CHAPTER III

Dengue

Richard B. Capps, M.D.

INTRODUCTION

Dengue is an acute febrile illness caused by a filterable virus transmitted by mosquitoes. It was first described by David Bylon in 1779 under the name of joint fever.[1] Since then, the disease has come to be recognized as common in many parts of the world, and a number of extensive epidemics have been described.[2] Bancroft,[3] in 1906, was the first to suggest that transmission might be due to *Aedes aegypti*. This was conclusively established by Cleland, Bradley, and McDonald in 1916 and 1919,[4] Siler, Hall, and Hitchens in 1926,[5] and Simmons, St. John, and Reynolds in 1931.[6] Subsequently, it was demonstrated that *Aedes albopictus*, *Aedes scutellaris*, and *Aedes hebrideus* [7] can also serve as insect vectors. That the etiological agent was a filterable virus was first proved by Ashburn and Craig in 1907.[8] In 1929, Blanc, Caminopétros, Dumas, and Saenz [9] found that certain species of monkeys could be infected with the virus and could thus serve as a natural reservoir. This was confirmed by Simmons, St. John, and Reynolds in 1931.

Although dengue is a nonfatal disease, it may assume considerable military importance because of its tendency to occur in massive outbreaks resulting in incapacity of large numbers of men. This type of epidemic is favored by the introduction of nonimmunes into an endemic area as so often occurred

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[1] Pepper, O. H. Perry: A Note on David Bylon and Dengue. Ann. M. Hist. 3: 363-368, September 1941.

[2] Sabin, Albert B.: Dengue. *In* Viral and Rickettsial Infections of Man. 2d edition. Philadelphia: J. B. Lippincott Co., 1952, pp. 556–568.

[3] Bancroft, T. L.: On the Etiology of Dengue Fever. Australas. M. Gaz. 25: 17, 1906.

[4] (1) Cleland, J. B., Bradley, B., and McDonald, W.: On the Transmission of Australian Dengue by the Mosquito Stegomyia Fasciata. M.J. Australia 2: 179–184, 1916. (2) Cleland, J. B., Bradley, B., and McDonald, W.: Further Experiments in the Etiology of Dengue Fever. J. Hyg. 18: 217, October 1919.

[5] Siler, J. F., Hall, M. W., and Hitchens, A. P.: Dengue: Its History, Epidemiology, Mechanism of Transmission, Etiology, Clinical Manifestations, Immunity and Prevention. Philippine J. Sc. 29: 1–304, January-February 1926.

[6] Simmons, J. S., St. John, J. H., and Reynolds, F. H. K.: Experimental Studies of Dengue. Philippine J. Sc. 44: 1–251, January-February 1931.

[7] (1) Daggy, R. H.: *Aedes scutellaris hebrideus* Edwards; A Probable Vector of Dengue in the New Hebrides. War Med. 5: 292–293, May 1944. (2) Mackerras, I. M.: Transmission of Dengue Fever by *Aedes* (*Stegomyia*) *scutellaris* Walk. in New Guinea. Tr. Roy. Soc. Trop. Med. & Hyg. 40: 295–312, December 1946. (3) Fairley, N. Hamilton: Medicine in Jungle Warfare, 26 Feb. 1945. [Official record.] (4) King, Willard V.: Notes on the Vectors of Dengue in New Guinea, February 1946. [Official record.]

[8] Ashburn, P. M., and Craig, C. F.: Experimental Investigations Regarding the Etiology of Dengue Fever. J. Infect. Dis. 4: 440–475, 1907.

[9] Blanc, G., Caminopétros, J., Dumas, J., and Saenz, A.: Recherches Expérimentales sur la Sensibilité des Singes Inférieurs au Virus de la Dengue. Compt. rend. Acad. d. Sc. 188: 468–470, 4 Feb. 1929.

during World War II. Since prophylactic measures were limited to mosquito control and since this was difficult to accomplish during combat, the disease was a definite military hazard throughout World War II in practically all areas of the Pacific and Asiatic theaters.

INCIDENCE

The incidence of dengue in the U.S. Army during World War II, by theaters of operations, is shown in table 3. It is evident that the disease was largely restricted to the Pacific and Asiatic theaters, although scattered cases were reported from each of the other theaters. The lack of a specific diagnostic test raises a question as to the validity of the diagnosis, especially where sporadic cases were reported. On the other hand, many cases were undoubtedly not recognized and were reported under the diagnosis of "fever of undetermined origin." It seems probable that the actual cases exceeded those reported. Finally, it should be noted that the incidence remained low throughout 1945. This was presumably due to improved mosquito control measures, although in certain areas an increased percentage of immunes may have also been a factor.

TABLE 3.—*Incidence of dengue in the U.S. Army, by area and year, 1942–45*

[Rate expressed as number of cases per annum per 1,000 average strength]

Area	1942–45		1942		1943		1944		1945	
	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate
Continental United States	35	0.00	(1)	(1)	12	0.00	14	0.00	9	0.00
Overseas:										
Mediterranean	97	0.07	(1)	(1)	82	0.19	13	0.02	2	0.01
Africa-Middle East	8	.05	4	.70	1	.02	2	.04	1	.02
China-Burma-India	7,753	17.92	143	25.14	1,150	24.96	4,050	25.39	2,410	10.84
Southwest Pacific	48,632	28.45	3,923	58.51	5,778	29.60	26,580	47.96	12,351	13.78
Pacific Ocean Area	27,365	23.67	12	.08	11,931	40.42	14,200	35.98	1,222	3.76
North America	1	.01	1	.02	(1)	(1)	(1)	(1)	(1)	(1)
Latin America	203	.53	117	1.14	39	.32	33	.38	14	.19
Total overseas	84,059	8.65	4,200	8.18	18,981	12.15	44,878	12.82	16,000	3.86
Total Army	84,094	3.46	4,200	1.38	18,993	2.82	44,892	5.98	16,009	2.25

[1] Troops present in the area; no cases reported.

NOTE.—0.00 indicates a rate of less than 0.005 per annum.

SPECIFIC OUTBREAKS

Australia

In March, April, and May of 1942, an extension epidemic of dengue occurred among U.S. Army troops stationed in Northern Territory and Queens-



U.S. Army photograph

FIGURE 2.—Capt. Thomas G. Graham, MC, Medical Inspector, Motor Transport Command No. 1, and Lt. Col. George H. Rohrbacher, MC, Surgeon, Motor Transport Command No. 1, in right foreground, inspect water for mosquito breeding patches, Breakaway Creek, Mt. Isa, Queensland, Australia, October 1942.

land (fig. 2). Approximately 80 percent of all U.S. personnel in this area were attacked within a period of about 3 months.[10] Epidemics were reported during January, February, and March of 1943 at Rockhampton and in the Brisbane area. Four hundred and sixty-three cases occurred among U.S. military personnel in the former outbreak.[11] A survey of Rockhampton during this period showed that 80 percent of more than 6,000 dwellings examined were breeding dengue-carrying mosquitoes. U.S. Army personnel required for mosquito control varied from 15 to 55 men; oil was supplied by the Rockhampton City Council (fig. 3).[12] The vector in Australia was *A. aegypti*.[13]

[10] Letter, Chief Surgeon, U.S. Army, Services of Supply, Southwest Pacific Area, to The Surgeon General, 15 Dec. 1942, subject: Medical Service in Australia, Section I: Sanitation and Vital Statistics.

[11] Quarterly Report, Surgeon, Base Section No. 3, U.S. Army, Services of Supply, Southwest Pacific Area, 27 Apr. 1943.

[12] Quarterly Report, Surgeon, I Corps, U.S. Army Forces in the Far East, 1 Jan. 1943-31 Mar. 1943.

[13] Essential Technical Medical Data, U.S. Army, Services of Supply, Southwest Pacific Area, for March 1944.



U.S. Army photograph

FIGURE 3.—*Enlisted men of the 109th Medical Battalion, 1st Division, spray a stagnant pond with kerosene guns to destroy larvae in mosquito control, Rockhampton, Australia, September 1942.*

New Hebrides and New Caledonia

An extensive epidemic of dengue occurred at Espiritu Santo between February and August 1943. Over 5,000 cases were reported in military personnel, representing approximately 25 percent of the base strength (table 1).[11] For several months prior to the onset of the epidemic, there had been widespread dumping of tin cans over the base without regard to sanitary regulations. This had resulted in heavy breeding of *A. aegypti* and *Aedes scutellaris hebridensis*. In June, with the epidemic still continuing, a complete mosquito survey of all camp areas and all territory within 500 yards of camp was instituted. All possible water containers, including tin can dumps, stored tires, oil drums, machinery, and tarpaulins were spotted on maps. A cleanup campaign was started employing approximately 300 men, 10 trucks, and other heavy equipment, and by August the epidemic was under control. It is noteworthy that very few cases occurred at this base during the succeeding rainy season in 1944.

[11] U.S. Malaria News Letter No. 11, Headquarters, Malaria Control Epidemic, Central South Pacific Area, September 1943. (Cited by Stevens, Frank W., Medicine in the South Pacific Area. Official record.)

TABLE 4.—*Incidence rates for dengue in U.S. Army personnel in New Caledonia and Espiritu Santo, from January to August, 1943 and 1944*

[Rate expressed as number of cases per annum per 1,000 average strength]

Month	New Caledonia		Espiritu Santo	
	1943	1944	1943	1944
January	1	1	----------	1
February	65	15	441	1
March	186	120	1,095	0
April	645	56	1,713	0
May	317	16	1,531	0
June	66	5	909	0
July	30	1	245	0
August	3	1	82	0

A less severe epidemic occurred at New Caledonia in 1943, as shown in table 4. The wide distribution of breeding places for *A. aegypti* and the lack of preventive measures by the resident population contributed to the persistence of the outbreak. The incidence of infection in military personnel would undoubtedly have been much higher if it had not been for intensive mosquito control measures carried out by the base malaria control unit. An epidemic was avoided, although cases developed during the 1944 rainy season.

Hawaiian Islands

In 1943, dengue appeared in Honolulu, T.H., in epidemic form for the first time in over 30 years. The evidence suggested that the disease was imported from Suva, Fiji Islands, where an epidemic was in progress. Two commercial airline pilots were hospitalized with dengue in Honolulu early in July 1943, shortly after arrival from Suva. One of the pilots was ill upon arrival whereas the other did not develop symptoms for several days and was not isolated by hospitalization until he had passed through the infectious period.[15] Three weeks later, two civilian cases appeared in the Waikiki Beach area of Honolulu, and, 12 days later, two cases occurred in Army personnel in the same section.[16] Measures were taken immediately to prevent an explosive outbreak, consisting chiefly of an extensive program of mosquito control. Also, proper screening of patients in hospitals and in homes was made mandatory, and large areas of the City of Honolulu were placed off limits to troops. Although 1,355 civilian cases were reported through 31 December 1943, only 56 cases occurred in military personnel.

[15] Gilbertson, W. E.: Sanitary Aspects of the Control of the 1943-1944 Epidemic of Dengue Fever in Honolulu. Am. J. Pub. Health 35: 261-270, March 1945.

[16] History of Preventive Medicine, United States Army Forces, Middle Pacific, pp. 231-235. [Official record.]

In order to render effective measures for control of mosquitoes in military areas, it was necessary to have adequate control in the surrounding civilian areas. Toward this end, the Army gave all possible assistance to civilian agencies. A medical officer was attached to the territorial board of health to make an epidemiological study of all new cases. Fifty enlisted men were assigned to spray the buildings and to eliminate breeding places of mosquitoes in homes where there were cases of dengue. Trucks, ladders, and spraying equipment were made available for use by civilian agencies. In September 1943, it became necessary to extend the program for mosquito control to include the entire City of Honolulu. The program was supervised by the U.S. Public Health Service, and labor was provided by a medical service company. Honolulu was divided into 3 districts and subdivided into 77 inspection zones, each of such size that one man could thoroughly cover his zone every 10 days.

Aedes mosquitoes were found breeding in all varieties of containers that could hold water, such as tin cans, bottles, barrels, jars, flower vases and cups, tanks, tubs, tires, storm drains, catch basins, unstocked fishponds, abandoned cesspools, and cisterns. Breeding places were also encountered in water-holding plants, such as spider lilies, pineapple lilies, and ape plants and in rotted-out holes and crotches in poinciana, algarroba, haole koa and guava trees, bamboo and banana stumps, and the larger water-holding pockets in traveler's palms. Other unusual breeding places were in fallen palm fronds and the holes of lava-formed rocks and pockets in emerged formations of coral reef. It is striking that in over one million inspections, on only four occasions were ground pools found to be breeding places for *Aedes* mosquitoes. Since both *A. aegypti* and *A. albopictus* have short flight ranges (up to 200 yards), it was only necessary to extend control operations to the fringes of the inhabited areas.

The effectiveness of these measures is shown in table 5. It will be noted that the breeding indices of *Aedes* mosquitoes were satisfactorily reduced. It

TABLE 5.—*Breeding index of* Aedes *mosquitoes in Honolulu, T.H., from August 1943 to August 1944*

Year and month	Index [1]	Year and month	Index [1]
1943		*1944*	
August	5.7	January	1.0
September	1.7	February	1.9
October	1.1	March	3.5
November	.9	April	1.8
December	1.2	May	1.0
		June	1.1
		July	.7
		August	.8

[1] Percentage of premises inspected in which *Aedes* larvae were found.

is interesting that the critical index or threshold of importance for dengue was 3.0 or less, which is considerably lower than the value of 5.0 which is generally accepted as the critical point for yellow fever.[17]

New Guinea and the Philippine Islands

From the onset of operations in New Guinea and adjacent islands, dengue was an important cause of noneffectiveness of troops.[18] Table 6 shows the case rates for the years 1944 and 1945; separate rates for this area are not available for the year 1943. It will be noted that the incidence was highest during January and February, which are the months of heavy rainfall. During the first 6 months of 1944, the case rates for dengue exceeded those for

TABLE 6.—*Incidence of dengue in U.S. Army personnel in New Guinea and adjacent islands, January 1944 to August 1945*

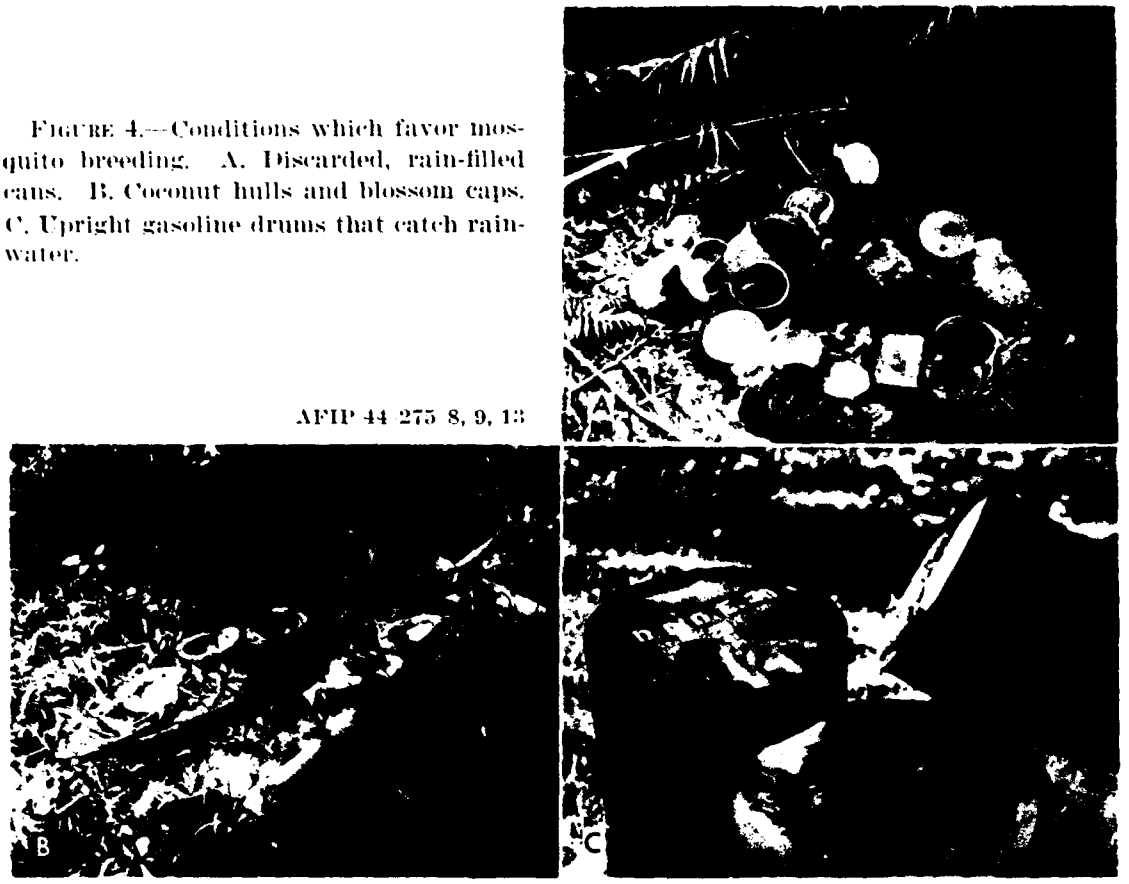
[Rate expressed as number of cases per annum per 1,000 average strength]

Year and month	Number of cases	Rate
1944		
January	3, 137	197. 6
February	2, 849	164. 1
March	2, 469	90. 6
April	1, 848	68. 0
May	1, 970	66. 1
June	2, 756	61. 2
July	2, 613	60. 1
August	1, 571	33. 6
September	1, 828	30. 5
October	1, 102	21. 5
November	935	23. 5
December	1, 001	23. 2
Total	24, 079	54. 2
1945		
January	640	24. 6
February	576	25. 8
March	597	25. 5
April	468	30. 5
May	353	27. 3
June	208	15. 3
July	48	6. 9
August	222	9. 2
Total	3, 112	21. 5

[17] Soper, F. L., and Wilson, D. B.: Species Eradication; A Practical Goal of Species Reduction in the Control of Mosquito-borne Disease. J. Nat. Malaria Soc. 1 (No. 1): 5–25, 1945.

[18] See footnote 7 (3), p. 52.

malaria. It will be noted that in 1945 the rates remained low, even during the rainy season. This presumably was due to improved mosquito control and to an increased percentage of immunes among military personnel. As occurred elsewhere, striking outbreaks appeared in certain units, notably in the Hollandia and Biak areas. In the Biak area, the ratio of dengue to malaria was 4:1.[19]



AFIP 44 275 8, 9, 13

FIGURE 4.—Conditions which favor mosquito breeding. A. Discarded, rain-filled cans. B. Coconut hulls and blossom caps. C. Upright gasoline drums that catch rainwater.

In New Guinea, the vector appeared to be *A. scutellaris*.[20] *A. aegypti* are rare in this area. This increased the problem of mosquito control because of the greater variety of breeding places employed by *A. scutellaris* (fig. 4). In addition, the day-biting habits of this species made individual protective measures necessary at all hours, especially in shaded jungle areas.

The situation in the Philippines is of particular interest because it illustrates the effectiveness of measures for controlling mosquitoes. Prior to World War II, dengue had always been a problem among Army forces stationed in the Philippines. Replacements frequently contracted the disease within a few months after arrival. Consequently, with the opening of the campaign for reoccupation, a serious situation was anticipated, especially

[19] Quarterly Report, Surgeon, I Corps, Southwest Pacific Area, 1 Apr. 1944-30 June 1944.
[20] See footnote 7 (4), p. 52.

during the rainy season in areas of dense population. However, in spite of the presence of large numbers of nonimmunes and the appearance of cases throughout the Philippine Islands, no real epidemic outbreaks developed. The case rates are shown in table 7.

TABLE 7.—*Incidence of dengue in U.S. Army personnel in the Philippine Islands, November 1944 to December 1945*

[Rate expressed as number of cases per annum per 1,000 average strength]

Year and month	Number of cases	Rate
1944		
November	652	39. 8
December	1, 360	49. 1
1945		
January	1, 033	32. 1
February	893	24. 8
March	1, 214	25. 7
April	857	19. 9
May	913	19. 6
June	839	13. 4
July	930	16. 4
August	1, 140	15. 2
September	439	7. 9
October	294	6. 3
November	285	6. 3
December	89	4. 1
Total for 1945	8, 926	15. 7
Total	10, 938	17. 9

Effective mosquito control was achieved by attaching malaria units to all forces operating in the Philippines. In addition to the usual control measures which were carried out on an intensive scale, area spraying with DDT (dichlorodiphenyltrichloroethane) from airplanes was carried out extensively over Manila (fig. 5) and other populated centers on Luzon Island during the early months of 1945.[21] The houses of natives adjacent to concentrations of troops were also sprayed with DDT.

It is of interest that reports from this area indicated considerable variation in the clinical picture. Thus, many cases showed only a single peak in temperature, and in many instances the disease was quite mild. The difficulties in diagnosis, particularly during the first few days of illness, were

21 Essential Technical Medical Data, U.S. Army Forces in the Far East, for March and April 1945. Inclosure 13, subject: *DDT Spraying in Luzon.*



U.S. Army photograph

FIGURE 5. Aerial view of Manila being sprayed against mosquitoes and flies with DDT insecticide by C-47's of a U.S. Air Force unit, Luzon, Philippine Islands, April 1945.

repeatedly pointed out. The disease was most commonly confused with malaria, acute infectious hepatitis, and scrub typhus.

Saipan

Perhaps the most extensive outbreak of dengue during World War II occurred in the Marianas Islands in the late summer of 1944. Relatively complete records are available only for Saipan. Shortly after the assault on this island, on 15 June 1944, dengue made its appearance among the troops. At first, the incidence was low, probably because the rainy season did not begin until the first of August and mosquitoes were not abundant. However, by 11 August, mosquitoes had become plentiful and the dengue rate had reached 300. The incidence continued to rise rapidly, and by 8 September the rate had reached approximately 3,500 per 1,000 per annum.[22]

This outbreak was obviously caused by the presence of large numbers of mosquitoes and the ineffectiveness of ordinary measures of control. Thus, there were innumerable breeding places provided by "an unbelievable amount

[22] Essential Technical Medical Data, U.S. Army Forces, Pacific Ocean Areas, for September 1944, Inclosure 4 thereto.

of rubble resulting from the total destruction of villages and scattered dwellings, a multitude of wells, cisterns, vats, troughs and rainwater-collection facilities as well as an immense quantity of tins, shell cases, et cetera." The difficulties encountered in controlling mosquitoes during and immediately following the assault phase of a campaign are sufficiently great under ordinary circumstances, but in this instance they proved to be insurmountable. This is illustrated by counts made of the number of mosquitoes found biting a single human during 10-minute periods. Thus, between 16 August and 10 September 1944, counts made in the late afternoon near the vicinity of towns or villages showed from 5 to 36 specimens of *A. aegypti* and from 2 to 16 specimens of *A. albopictus* as well as 1 to 7 specimens of other species. Counts made at night showed as many as 42 specimens of still other species.

Effective control of mosquitoes only became possible when a supply of DDT arrived on 3 September 1944. Area control was employed by spraying 5 percent DDT and kerosene from airplanes. It was found that small planes were inadequate and that it was necessary to use C–47's because of the size of the area involved. Between 12 and 22 September, 8,600 gallons of the mixture was sprayed over a total of approximately 15,000 acres, an average of approximately two-tenths of a pound of DDT per acre. In addition, DDT residual spray was used in all tents and living quarters of hospitals.[23] This was accomplished with a truck-mounted power spray unit for chemical decontamination provided by the Chemical Warfare Service.

The effectiveness of these measures is shown in table 8. The number of new cases began to decrease significantly about 1 week after the aerial spraying of DDT was started. After the first of October, the number of new cases was less than 10 percent of the number which occurred at the height of the epidemic. Although the preliminary summary reports show only 10,834 cases of dengue for the entire Pacific Ocean Area during August, September, and October, 1944, it is reliably estimated that there were 20,000 cases on Saipan alone.[24] This discrepancy was probably due to a high percentage of cases that were cared for in quarters and were not officially reported.

The effectiveness of these measures in controlling the mosquito population was clearly demonstrated by observations on the "biting rate" per minute. Thus, surveys made before and after spraying by airplane indicated a decrease up to 98 percent. In addition, it was generally agreed by troops that there had been a tremendous reduction in the mosquito population. This was further substantiated by surveys of breeding places of mosquitoes made before and after DDT spraying. Finally, the effectiveness of these measures is indicated by the marked decrease in new cases of dengue which occurred before the end of the rainy season and at a time when susceptible troops were still arriving on the island.

[23] Letter, Deputy Surgeon, Headquarters, U.S. Army Forces, Pacific Ocean Areas, to Surgeon, Pacific Ocean Areas, 30 Sept. 1944, subject: Measures Used for Control of Dengue Fever on Saipan.

[24] Annual Report, Eighteenth Medical General Laboratory, Pacific Ocean Areas, 1944. Inclosure 5 thereto.

TABLE 8.—*Daily report of new cases of dengue at height of the epidemic in Saipan, 14 September to 6 October 1944*

Date	Number	Date	Number
1944		*1944*	
September 14	393	September 26	62
15	426	27	87
16	294	28	79
17	306	29	71
18	289	30	44
19	275	October 1	36
20	230	2	33
21	137	3	27
22	137	4	28
23	112	5	32
24	93	6	23
25	81		

China-Burma-India

Although dengue was endemic in most of the China-Burma-India theater, the majority of cases among U.S. troops occurred in the region of Calcutta, India. The highest incidence appeared between July and October with the peak varying according to the dates of the monsoon.[25] During 1942, 1943, and 1944, the dengue rates were approximately the same; namely, 25 per 1,000 per annum. However, in 1945, the rate dropped to less than half. Although the explanation for this is not entirely clear, it is felt that the improvement was largely due to the work of malaria control detachments whose measures were directed towards *Aedes* mosquitoes as well as the *Anopheles* mosquitoes. In addition, antimosquito supplies and equipment were more readily available in 1945 and individual protective measures were better enforced (fig. 6).

One small but sharp outbreak of dengue which occurred in the China theater illustrates the military importance of this disease as follows: During September 1945, after V–J Day, an epidemic was reported in Hankow, China, which was said to have affected 80 percent of the population of the city. When American forces occupied the airport, 40 of the first 48 men to arrive contracted dengue within 5 to 10 days.[26] Because of this situation, it was first recommended that operations from Hankow be suspended. Subsequently, however, they were considered essential. Intensive measures for

[25] Van Auken, H. A.: A History of Preventive Medicine in the United States Army Forces of the India-Burma Theater, 1942 to 1945, p. 317. [Official record.]

[26] Essential Technical Medical Data, U.S. Forces, China Theater, for October 1945.



U.S. Army photograph

FIGURE 6. A train medical officer (holding box) distributes enough mosquito repellent to car commanders for them to issue one bottle per man in their cars. Immediate distribution is made to insure each man having adequate antimalarial protection prior to departure of train from port at Bombay, India, March 1945.

mosquito control were undertaken, the city of Hankow was declared out of bounds, and personal protective measures were rigorously enforced. The effectiveness of these steps was indicated by an absence of further cases among U.S. military personnel.

CLINICAL MANIFESTATIONS

Variations in the character and severity of dengue have long been recognized as dependent upon differences in particular outbreaks and upon inherent and acquired degrees of individual resistance.[27] The variabilities of this disease in civilian populations have been discussed in detail elsewhere[28]

[27] Lumley, G. F.: Dengue. Service Publication No. 3, Commonwealth of Australia, Department of Health, 1943.

[28] (1) Simmons, James Stevens: Dengue Fever. *In* Virus and Rickettsial Diseases. A Symposium Held at the Harvard School of Public Health, June 12-June 17, 1939. Cambridge, Massachusetts, Harvard University Press, 1940, pp. 349-364. (2) Simmons, J. S.: Dengue Fever. M. Clin. North America 27: 808-821, May 1943. (3) See footnote 2, p. 50.

and provide a comprehensive background for the military cases described in different parts of the Pacific area. These were likewise of varying severity and symptomatology,[29] and in some instances, because of lack of specific laboratory tests, the diagnosis could be only denguelike fever[30] based on symptomatology and epidemiological considerations.

Characteristically, the onset of dengue was sudden, accompanied by fever and sometimes by a chill. The fever was of two types—saddleback and single phase. Patients were usually admitted to the hospital within a few hours of onset of the disease, with a temperature ranging from 99° to 104° F. which persisted for at least 2 or 3 days.[31] Over half the patients then had a remission in which both the fever and symptoms practically disappeared. This remission lasted 1 or 2 days and was followed by a second rise in temperature and return of symptoms. These, in turn, subsided rapidly on the fifth to seventh day of illness. In patients who did not exhibit this saddleback type of fever, symptoms and fever were largely the same but persisted for several days, regressing gradually from the third to the eighth day of illness.

Dizziness, prostration, and extreme weakness in the legs were frequent presenting symptoms. Frontal or occipital headache, generalized aching especially in the back and joints, and pain in and around the eyes developed early. Anorexia was common and was often accompanied by nausea and sometimes by vomiting. Occasionally, mild abdominal pain was noted. Many patients complained of insomnia and restlessness, and these symptoms frequently persisted into convalescence.

Flushing of the face and neck and scleral injection were common. Two types of rash were observed. One, an enanthem, appeared within the first 12 hours, if at all, and consisted of pinpoint-sized, discrete, glistening vesicles on the posterior half of the soft palate. Star-shaped redness developed beneath these within 24 hours. This rash was morbilliform; it faded during the period of remission and did not recur with the second rise in temperature. The other type of rash was an exanthem (fig. 7). Seventy-nine percent of the patients in one group had this rash on admission to hospital. It could be mild (a few discrete, light pink, morbilliform spots on the sides of the thorax, inner surfaces of the upper arms, and in the lumbar region) or severe when it presented unbroken, erythematous areas covering the face below the forehead, neck, shoulders, and thorax. The morbilliform charac-

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[29] (1) Diasio, J.S., and Richardson, F. M.: Clinical Observations on Dengue Fever; Report of 100 Cases. Mil. Surgeon 94: 365–369, June 1944. (2) Kisner, P., and Lisansky, E. T.: Analysis of an Epidemic of Dengue Fever. Ann. Int. Med. 20: 41–51, January 1944.

[30] (1) Fairchild, L. M.: Dengue-Like Fever on the Isthmus of Panama. Am. J. Trop. Med. 25: 397–401, September 1945. (2) Johnson, J. A., Jr., Martin, W. B., and Breslow, L.: Dengue-Like Fever on Okinawa. Bull. U.S. Army M. Dept. 5: 306–311, March 1946.

[31] (1) See footnote 29, p. 72. (2) Cavanagh, J. P.: Dengue; Observations on the Disease as Seen in the South Pacific Area. War Med. 4: 549–555, December 1943.



AFIP E-4438-5, 7

FIGURE 7. Rash of dengue fever on chest and back.

ter became apparent at the edges of the confluent areas, notably the lower half of the upper arm, upper part of the abdomen, and thoracic extensions of the axillary spaces. This rash also faded during remission but recurred, usually in less intense form, with recrudescence of fever. When it extended to the palms of the hands and soles of the feet, it was frequently followed by itching.

The incidence of adenopathy was highly variable and, when present, it most commonly involved the cervical nodes,[32] persisting through the second phase of fever and subsiding gradually during convalescence. Bradycardia was usually present and first appeared after the second day of illness, sometimes lasting into convalescence. Leukopenia was present early, with an average reduction in number of white blood cells to 5,450 per cubic millimeter. By the fifth day of illness, the average count numbered 3,500 cells per cubic millimeter, with a relative lymphocytosis. Atypical lymphocytes with vacuolated cytoplasm and coarse granular inclusions were commonly seen. The symptoms and signs of disease in two groups of patients in the U.S. Army are recorded in table 9.

TABLE 9.—*Physical signs and symptoms of 418 cases of dengue in two groups of U.S. Army patients, 1944*

Condition	Australia (percent)	South Pacific (percent)
Physical signs:		
Fever	100	97
Saddleback	55	66
Single temperature rise	45	30
Intermittent temperature rise	0	1
Afebrile	0	3
Rash	79	37
Flushing of face (initial phase)	33	26
Tongue coated	53	----
Bradycardia (after 2d day)	----	97
Scleral injection	89	26
Eyeball tenderness to pressure	45	----
Adenopathy	100	17
Cervical	94	[1] 93
Epitrochlear	90	
Inguinal	80	
Laryngeal or oropharyngeal vascular congestion	17	11
Leukopenia	----	100
Red blood cell count	Normal	Normal
Febrile albuminuria		8
Symptoms:		
Feverishness	100	97
Chills or chilliness	54	32

[32] See footnote 29, p. 72.

TABLE 9.—*Physical signs and symptoms of 418 cases of dengue in two groups of U.S. Army patients, 1944*—Continued

Condition	Australia (percent)	South Pacific (percent)
Symptoms—Continued		
Aches and pains	----------	99
Headache	94	69
General aching	75	35
Lumbar backache	89	43
Orbital pain	74	25
Anorexia	85	----------
Loss of taste	55	----------
Bitter taste	45	4
Weakness (early)	29	14
Insomnia	53	6
Coryza (fleeting)	24	----------
Sore throat (mild)	12	3
Stiff neck	14	----------
Dizziness and nausea	29	----------
Constipation	2	2
Pruritus	20	3
Photophobia	----------	5
Total number of patients	100	318

[1] Of those with adenopathy; 16 percent of the total group (318 cases).

Source: (1) Diasio, J. S., and Richardson, F. M.: Clinical Observations on Dengue Fever; Report of 100 Cases. Mil. Surgeon 94: 365-369, June 1944. (2) Kisner, P., and Lisansky, E. T.: Analysis of an Epidemic of Dengue Fever. Ann. Int. Med. 20: 41-51, January 1944.

The disease ran its course in 6 to 10 days (average hospital stay 7½ to 9 days) with complete recovery. In general, symptoms tended to abate with the fever, but during convalescence some degree of neurasthenia manifested by muscular weakness, lack of ambition, mental depression, insomnia, and anorexia was almost invariable. These usually disappeared in 7 to 14 days, but sometimes lasted much longer.[33] Recurrences were rare and could probably be explained as re-infections.

Occasional complications of dengue were observed, including hemorrhagic nephritis, trismus of the jaw, arthritis of hip, suppuration of glands, persistent bradycardia, and purpuric manifestations.[34] Urogenital complications were also occasionally observed. Dull testicular pain and impotence were not infrequent during convalescence, and the latter was attributed to generalized weakness.[35] In one group of 141 patients, 8 men

[33] (1) See footnotes 29, p. 72; and 31 (2), p. 72. (2) Hyman, A. S.: The Heart in Dengue; Some Observations Made Among Navy and Marine Combat Units in the South Pacific. War Med. 4: 497-501, November 1943.

[34] See footnote 31 (2), p. 72.

[35] Weyrauch, H. M., and Gass, H.: Urogenital Complications of Dengue Fever. J. Urol. 55: 90-93, January 1946.

(5.7 percent) had late involvement of the urogenital tract, including orchitis, with subsequent atrophy of the testis and repeated bloody seminal emissions. Rare neurological complications following dengue were described by Kaplan and Lindgren[36] who reported palsy of the facial, palatine, long thoracic, ulnar, peroneal, and sciatic nerves.

Dengue may be confused with rubella because of the rash and because of the type of cervical adenopathy observed. Other diseases frequently considered in differential diagnosis included scarlet fever, infectious mononucleosis, malaria, viral pneumonia, influenza, and occasionally meningitis. A knowledge of the epidemiology of dengue and its clinical course was helpful in early diagnosis.

Sufficient discrepancies in signs and symptoms existed in certain outbreaks of denguelike fever to question the diagnosis. In 32 cases from Panama,[37] the symptoms and course of the disease were similar to dengue except that the typical rash was not seen, bradycardia did not occur, and the incidence of lymphadenopathy was low. Definite diagnosis was impossible because of lack of laboratory methods. Many of the patients observed in Okinawa in 1945 likewise had most of the diagnostic signs of dengue.[38] The clinical picture presented by these cases was remarkably uniform. Specifically noted was the sudden onset, with chilly sensations, rapid rise in temperature, headache, pain on movement of the eye, postorbital pain, photophobia, generalized aching, periarticular soreness, conjunctivitis, lymphadenopathy, bradycardia, and hematological changes. However, it was pointed out that the short duration, relative infrequency of recrudescence of fever and symptoms, and the absence of rash in these patients were against the diagnosis of dengue. Later, Sabin,[39] on the basis of failure to produce dengue in four human volunteers inoculated with serum from five of these patients, suggested that this outbreak may have been leptospiral meningitis.

The treatment of dengue was symptomatic. Codeine (½ to 1 gr.) and acetylsalicylic acid (10 gr.) usually sufficed for relief of pain,[40] and phenobarbital (1½ gr.) was employed for insomnia and restlessness. Morphine was rarely required.

SCIENTIFIC INVESTIGATIONS

The military importance of dengue became evident early in World War II. As a result, the Commission on Neurotropic Virus Diseases, Army Epidemiological Board (Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army), became interested in

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[36] Kaplan, A., and Lindgren, A. J.: Neurologic Complications Following Dengue. U.S. Nav. M. Bull. 45: 506 510, September 1945.

[37] See footnote 30 (1), p. 72.

[38] See footnote 30 (2), p. 72.

[39] Sabin, A. B.: Research on Dengue During World War II. Am. J. Trop. Med. 1: 30 50, January 1952.

[40] See footnote 31 (2), p. 72.

promoting research in this field with the specific objectives of producing a protective vaccine and, if possible, of developing a specific diagnostic procedure. Neither of these was available before World War II, for up to that time the virus had not yet been definitely propagated in animals or in tissue culture. Lt. Col. Albert B. Sabin, MC, was the central figure in the series of studies which provided pertinent key information. Detailed reports of his findings are available elsewhere.[41] The following summarizes those findings especially pertinent to military medicine:

1. Proof of the existence of multiple immunological types. Seven strains of dengue virus were isolated from patients who contracted their illness in Hawaii, New Guinea, and India. Serum obtained during the first 48 hours of the disease was shipped to the United States under refrigeration and inoculated into volunteers who had never resided in areas where dengue is endemic. Subsequently, studies of transmission by mosquitoes were conducted with *A. aegypti.* The existence of separate strains was demonstrated both by studies of cross-immunity and through virus neutralization tests using immune serum. At least two immunologically distinct types of virus were identified. It was shown that the Hawaiian strain, one of the four New Guinea strains, and the two Indian strains were identical. Thus, two separate strains were detected in New Guinea.

2. The long persistence of immunity to homologous types of virus. It was found that homologous immunity persisted for at least 18 months under conditions which precluded reinforcement of immunity by subclinical reinfection. Heterologous immunity was observed but persisted for only about 2 months.

3. The modifications of the clinical manifestations of the disease which result from reinfection with a heterologous type of virus at various periods after the primary attack. It was shown that a superimposed heterologous infection produced marked variations in the course of the disease depending upon the time which lapsed from the primary infection. A short febrile illness of 2 days' duration with or without rash, lymphadenopathy, or other characteristic manifestations occurred under these circumstances. In these experimental cases, the virus, recovered from the blood showed conclusively that the observed disease actually was dengue. This knowledge readily explained the many cases reported of the transitory acute illnesses which could not be specifically identified, particularly from New Guinea. This explanation is confirmed further by the fact that two of the New Guinea samples of serum from individuals with this type of illness produced the

41 (1) See footnotes 2, p. 50; and 39, p. 76. (2) Sabin, A. B., and Schlesinger, R. W.: Experimental Studies on Human and Mouse Adapted Dengue Virus. Paper presented at joint meeting of American Society for Experimental Pathology and American Association of Immunologists, Atlantic City, N.J., 13 Mar. 1946. (3) Letter, Maj. Albert B. Sabin, MC, to Preventive Medicine Service, Office of the Surgeon General, 3 Aug. 1944, subject: Isolation of Several Strains of Dengue Virus From Serum of Patients With Various Types of Fevers in New Guinea. (4) Sabin, A. B., and Schlesinger, R. W.: Production of Immunity to Dengue With Virus Modified by Propagation in Mice. Science 101: 640-642, 22 June 1945.

classical picture of dengue when inoculated into nonimmune volunteers in the United States.

4. The demonstration that type-specific immunity to dengue is associated with neutralizing antibodies for the virus. It was shown that the demonstration of neutralizing antibodies can be employed for diagnostic and epidemiological survey purposes. They should prove to be of great value in the future.

5. The propagation of dengue virus in mice. Sabin finally succeeded in propagating the virus in mice. In the course of a number of passages, the virus underwent a mutation since it lost its capacity to produce severe illness in man but retained its capacity to produce a rash. A mousebrain extract of this modified virus was found to afford complete protection against the naturally acquired disease. A single mousebrain was shown to contain at least 10,000 immunizing doses which led to the preparation of an effective lyophilized vaccine. Unfortunately, large-scale field trials were not undertaken because the opportunities for testing the vaccine ceased with the ending of the war.

6. Investigations of dengue, conducted by Colonel Sabin in Panama, showed clearly that dengue has occurred there since 1941 and suggested that the interior of Panama may be an endemic focus of the disease.

In conclusion, it should be pointed out that the history of dengue during World War II reflects great credit on the U.S. Army Medical Department. Like some other virus diseases, dengue was promoted to the category of an illness diagnosable by laboratory means and preventable.

CHAPTER IV

Neurotropic Virus Diseases

John R. Paul, M.D.

The group of diseases designated as neurotropic virus diseases in this chapter has been selected, for practical reasons, on a somewhat arbitrary basis. They include acute infections with the viruses that cause the arthropodborne virus encephalitides: poliomyelitis, rabies, and lymphocytic choriomeningitis. It is with some aspects of the clinical and epidemiological story of these virus infections, as they occurred in military personnel in World War II, that this chapter is concerned.

Numerically speaking, the recognized military cases of neurotropic virus infections have been insignificant, but from other standpoints these diseases have proved to be of some military importance. In the first place, any virus disease that attacks the central nervous system easily acquires a bad reputation. Furthermore, as a group, the mortality is apt to be high and the stigma of injured brain function accompanies them. In the case of poliomyelitis, not only does this disease carry a more serious prognosis when it occurs in young adults (of military age) than in children, but when a permanent Army post is involved, this disease presents a threat to dependents who may happen to be living within the epidemic area. And finally, as far as the arthropodborne virus encephalitides are concerned, any mosquitoborne disease is of military significance.

Early in World War II, the Medical Department of the U.S. Army recognized that this relatively new group of diseases might pose a number of problems, and to forestall them, Circular Letter No. 74 was issued on this subject by the Surgeon General's Office on 19 March 1943. This circular was followed by War Department Technical Bulletin (TB MED) 212, issued 16 January 1946. The bulletin reviewed information bearing on the common neurotropic virus diseases of man, including classification and diagnostic features. In addition, the bulletin described the circumstances under which the then available diagnostic procedures could be profitably utilized.

THE ARTHROPODBORNE VIRUS ENCEPHALITIDES

The arthropodborne virus diseases comprise a group whose membership has expanded greatly since the war, but even in 1941 the recognized members were eastern and western types of equine encephalomyelitis, St. Louis encephalitis, Japanese B encephalitis, and Venezuelan encephalitis. Others of less importance to U.S. Forces included Russian spring-summer encepha-

litis (and other types from Russia and Siberia), some types from Africa, and louping ill from England. These will not be considered here.

The number of military cases of this group of diseases which occurred in World War II turned out to be few indeed, but besides the reasons already given that these few cases deserve attention here is that research initiated and promoted by the Preventive Medicine Division, Office of the Surgeon General, and the Army Epidemiological Board (Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army), contributed materially to the addition of knowledge about these important infections during World War II.

Military History Prior to World War II

In view of the fact that no member of this group of arthropodborne virus encephalitides had been discovered, nor had the diseases which they cause been recognized as such prior to the 1930's, there is nothing about them in the medical history of World War I; nor had there been in the post-World War I period any experience by the Armed Forces with these agents or with the diseases they cause. If cases of this group of illnesses had occurred and attracted attention in 1917–18, they would probably have been listed under the miscellaneous group of "encephalitis, type undetermined" or perhaps as "epidemic encephalitis." During the last year of World War I and the years immediately following, the type of encephalitis most frequently encountered in military populations was encephalitis lethargica, otherwise known as Von Economo's disease. The records from World War I show 80 admissions, and at least 79 secondary cases of encephalitis, reported for the period from 1 April 1917 to 31 December 1919 in the total U.S. Army of approximately 4 million.[1] In this group, 27 deaths occurred, giving a case fatality ratio of about 17 percent. The chances that a large percentage of these cases were examples of encephalitis lethargica are good. However, as the etiological agent of that disease was never established, one cannot speak with any confidence that it was actually a virus disease and therefore deserves discussion here. Furthermore and fortunately, the incidence of encephalitis lethargica began to decline in the midtwenties, both in the United States and in Europe. By 1930, to all intents and purposes, classical cases of this disease had disappeared, so for the present at least, we need not pursue the discussion about it further, except to point out that other new types of encephalitis were soon to supplant Von Economo's disease.

It was during the 1930's that the arthropodborne virus encephalitides came under scrutiny, the first recognition of any member of the group being that of the virus of western equine encephalomyelitis, isolated with some difficulty, from a sick horse in California in 1931 by Dr. Karl F. Meyer of the University of California, San Francisco. Later, Dr. Carl TenBroeck, of the

[1] The Medical Department of the United States Army in the World War. Washington: Government Printing Office, 1925, vol. XV, pt. 2, pp. 90 138, 656.

Rockefeller Institute of Medical Research at Princeton, N.J., found that strains of the equine encephalomyelitis viruses could be separated into eastern and western types. The "disease" for which these viruses were responsible was regarded at that time primarily, if not entirely, as one of horses. A manifest interest by the Army in this matter accompanied the report in 1934 by Lt. Col. (later Brig. Gen.) Raymond A. Kelser, VC, that these viruses could be transmitted from horse to horse by certain species of mosquitoes.

A second chapter in the story was written when it was found that this type of illness affected man. In 1933, a severe outbreak of human encephalitis occurred in and about the city of St. Louis, Mo. More than 1,000 human cases were reported with about an 18 percent mortality. The virus of St. Louis encephalitis was isolated in this epidemic more or less coincidentally by Drs. Ralph S. Muckenfuss and L. T. Webster. Although sick horses received little notice during this epidemic, some of the investigators, including Maj. (later Brig. Gen.) James S. Simmons, MC, thought that St. Louis encephalitis might be related to one of the equine encephalitides and attempted to infect horses with the St. Louis virus. The assumption was correct, and the failure to substantiate it experimentally at that time might have been due to the fact that the horses used were from the St. Louis area and they could well have been immune to the disease.

It was also at about this time (1933–34) that U.S. investigators began seriously to compare the St. Louis epidemic with the existing situation in Japan where endemic encephalitis had appeared in parts of the home islands almost every summer since 1871. In 1924, there had been a particularly bad epidemic, and clinical studies had made it possible for the Japanese to distinguish their diseases from epidemic encephalitis of the so-called A type (Von Economo's disease). For this reason, Japanese epidemic encephalitis has been termed type B encephalitis. The epidemic of 1924 had spread through a wide area resulting in a heavy mortality among 6,000 reported cases. During the period from 1924 to 1937, outbreaks occurred almost every summer in Japan, resulting in a total of some 21,000 reported cases for that period with the heaviest concentration of cases occurring in the region of the Inland Sea. Similar recurrent appearances of summer or autumn encephalitis were known to have been reported from the Ryukyu Islands, as well as from Formosa, Manchuria, and the far eastern maritime districts of Soviet Russia. Opinion in Japan was divided as to the means of spread, and by 1938, although one group had suspected that it was mosquitoborne, the balance of Japanese medical opinion held to the view that it was spread from the respiratory tract.

By 1938–39, relations between Japanese medical science and that of the United States could hardly be described as close and shortly thereafter ceased altogether. Consequently, the up-to-date story on current Japanese views as to how their type of encephalitis was transmitted and just where this disease could be expected to appear was not readily available to medical intelligence officers during the war years.

The next development in this story took place in the United States in 1938, with the appearance in Massachusetts, Rhode Island, and Connecticut of a less extensive outbreak of acute encephalitis involving both man and horses. The causative virus was identified as eastern equine encephalomyelitis virus. It also became apparent that here was a group of diseases that not only infected both man and horses, but perhaps other animals. More or less coincidentally, the discovery in 1937 of the spring-summer type of encephalitis in the forested, far eastern regions of the U.S.S.R. and the demonstration that it was caused by a new virus which was tickborne, all indicated the existence of a large group of related agents extremely widespread geographically and with a variegated group of insects (arthropods) as vectors and several mammalian hosts. To this group were soon added other strains of virus from South America (notably Venezuelan encephalitis), and subsequently several from Africa.

Early in the 1940's, information about these diseases was accumulating at a rather rapid rate, although much of it was still theory. Birds had been found to be infected, which made the epidemiological picture still more complicated. Eventually, the epidemiology of some of this group of diseases, as they occurred in the United States, was worked out largely through the efforts of Dr. William McD. Hammon at the University of California, San Francisco. From his work, the concept gradually emerged that, in this country at least, this group of infections, many of which were inapparent, was primarily one of birds and that the severe infections in man, horses, and other animals were what might be called casual, though spectacular, accidents. Apparently, the avian infection could be very widespread numerically but was mild, causing little more than a viremia in certain members of the avian family. It was transmitted to various species of both birds and mammals usually through the agency of *Culex* mosquitoes.

This then was the background in 1941 with regard to the "new" neurotropic virus infections with which the U.S. Army might be confronted if it should engage in global combat. The threat was appreciable in that any mosquitoborne disease recalled the destructive effect which malaria, yellow fever, or dengue had had upon troops in the field in the past. In addition, a number of potential theaters of war, such as Japan, Manchuria, and elsewhere, were listed as endemic or epidemic areas and might possibly turn out to be hotbeds of infection by one of the worst members of the group, Japanese B encephalitis. These potentialities were further emphasized by an epidemic of western equine encephalomyelitis which swept over a large section of Western Canada and many areas in the Western United States, including the Dakotas, Montana, and Colorado in the summer of 1941. Thousands of civilian cases occurred, although the number of U.S. Army personnel involved in this epidemic was insignificant. However, in Canada where it was estimated that there were more than 5,000 cases, mostly in Saskatchewan and Manitoba, the epidemic had also involved certain training areas where Canadian troops were stationed, and during the summer of 1941, a number of cases occurred in the

Canadian Army.[2] It hardly could be questioned in the autumn of 1941 that here was a new disease of potential military importance to U.S. troops.

Diagnosis.—It is important to mention here that not only in 1917–18 but in the subsequent 25 years the clinical diagnosis of encephalitis proved to be a loose one indeed, covering a number of different entities. In another volume in the history of the Medical Department in World War II, Sabin states:[3]

> Clinical records from civilian as well as military medical practice indicate that the diagnosis of encephalitis is commonly made whenever clinical manifestations suggestive of cerebral disturbance (ranging from mild lethargy to coma, from slight delirium to complete disorientation, from restlessness to convulsions) are associated with an otherwise undiagnosable febrile illness. The diagnosis is not infrequently made when the syndrome of aseptic meningitis is associated with what may be interpreted as lethargy or unusual restlessness. It is made not only when the cerebral disturbance is associated with pleocytosis, but also in its absence, and indeed not infrequently when toxic encephalopathy is associated with certain bacterial infections.

In the period 1941–46, and subsequently, the exact method of making a diagnosis of this group of virus diseases was by immunological and virological tests. Some of these became available during and immediately prior to World War II. However, the utilization of these tests, which included neutralization or complement fixation tests on matched specimens of sera, was more or less in its infancy and hardly more than half a dozen laboratories in the United States capable of carrying them out.[4]

Experience During World War II

Most, although not all, of the apprehension about arthropodborne virus encephalitides proved to be unnecessary, for when the Second World War was over the incidence of these infections in military personnel turned out to be small. There were no large wartime epidemics in the United States involving the civilian population compared to those at St. Louis in 1933 and in the Northwest in 1941.

The final experience in World War II with these diseases both as to number of recognized cases, incidence rates, and deaths ascribed to encephalitis is listed in tables 10 and 11. It is clear that the figures suffer somewhat from the inaccuracies of diagnoses which are apt to beset all figures on the incidence of the encephalitides, infectious or otherwise. As just mentioned, Sabin has pointed out that the clinical diagnosis of any kind of encephalitis

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[2] Report, Commission on Neurotropic Virus Diseases, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, 1 Dec. 1941–1 May 1942.

[3] Sabin, Albert B.: Encephalitis. *In* Medical Department, United States Army. Preventive Medicine in World War II. Volume VII. Communicable Diseases: Arthropodborne Diseases Other Than Malaria. [In preparation.]

[4] Better known laboratories readily available to the Medical Department of the U.S. Army for the diagnostic purpose of these diseases, in 1941–45, included that of the Army Medical School, Washington, D.C., the G. W. Hooper Foundation of the University of California in San Francisco, the Rockefeller Institute for Medical Research in New York City (both of which facilities were made available through the Commission on Neurotropic Virus Diseases of the Army Epidemiological Board), and a few other laboratories, also connected with the Army through that Board.

without the assistance of serological tests is notoriously difficult. In view of the fact that such immunological tests were not available in many of the cases occurring in military personnel during wartime, the data in tables 10 and 11 must be regarded as being approximate rather than definitive. It should be noted, however, that the rates for infectious encephalitis were higher in 1944 and 1945 in the Pacific than in Europe. This is what should have been expected because, except for the presence of tickborne Russian spring-summer encephalitis in Czechoslovakia and in eastern Austria, the arthropodborne encephalitides as they are now known to occur in man are almost entirely absent from Europe.

TABLE 10.—*Admissions for encephalitis in the U.S. Army, by diagnosis, selected area, and year, 1942–45*

[Preliminary data based on sample tabulations of individual medical records]
[Rate expressed as number of admissions per annum per 1,000 average strength]

Diagnosis and area	1942–45		1942		1943		1944		1945	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Infectious encephalitis: [1]										
Continental United States	187	0.01	44	0.02	65	0.01	43	0.01	35	0.01
Overseas:										
Europe	(72)	0.02	(1)	0.01	(6)	0.02	(20)	0.01	(45)	0.02
Pacific	(107)	.03	(1)	.00	(5)	.01	(41)	.04	(60)	.04
Total overseas	247	0.02	4	0.01	14	0.01	94	0.02	135	0.03
Total Army	434	0.02	48	0.01	79	0.01	137	0.02	170	0.02
Postvaccinal encephalitis: [2]										
Continental United States	[3]	[3]	[3]	[3]	[3]	[3]	1	0.00	.....	0.00
Overseas:										
Europe	[3]	[3]	[3]	[3]	[3]	[3]	.....	0	.....	0.00
Pacific	[3]	[3]	[3]	[3]	[3]	[3]	(6)	.01	(5)	.00
Total overseas	[3]	[3]	[3]	[3]	[3]	[3]	6	0.00	10	0.00
Total Army	[3]	[3]	[3]	[3]	[3]	[3]	7	0.00	10	0.00
Encephalitis, other and undetermined: [4]										
Continental United States	953	0.06	272	0.10	355	0.07	211	0.05	115	0.04
Overseas:										
Europe	(89)	0.02	(9)	0.11	(10)	0.04	(20)	0.01	(50)	0.02
Pacific	(138)	.04	(7)	.03	(17)	.04	(19)	.02	(95)	.07
Total overseas	394	0.04	26	0.04	101	0.06	97	0.03	170	0.04
Total Army	1,347	0.05	298	0.09	456	0.07	308	0.04	285	0.04

[1] Includes infectious encephalomyelitis and Japanese B type encephalitis as well as other types of infectious encephalitis. Excludes lymphocytic choriomeningitis.

[2] Includes postvaccinal encephalomyelitis.

[3] Data are not available.

[4] Includes encephalomyelitis, other and undetermined. Excludes lymphocytic choriomeningitis.

NOTE.—Figures in parentheses are subtotals.

TABLE 11.—*Deaths due to encephalitis in the U.S. Army, by diagnosis, selected area of admission, and year of death, 1942–45*

[Preliminary data based on tabulations of individual medical records]
[Rate expressed as number of deaths per annum per 100,000 average strength]

Diagnosis and area	1942–45		1942		1943		1944		1945	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Infectious encephalitis: [1]										
Continental United States	9	0.06	2	0.08	2	0.04	3	0.08	2	0.07
Overseas:										
Europe	(4)	0.09	.....	0	.....	0	(1)	0.06	(3)	0.13
Pacific	(3)	.10	.....	0	.....	0	(2)	.20	(1)	.07
Total overseas	12	0.11	1	0.17	.....	0	6	0.16	5	0.11
Total Army	21	0.08	3	0.03	2	0.03	9	0.12	7	0.09
Postvaccinal encephalitis: [2]										
Total Army	(3)	(3)	(3)	(3)	(3)	(3)	.....	0	.....	0
Encephalitis, other and undetermined: [4]										
Continental United States	57	0.39	7	0.26	20	0.39	23	0.58	7	0.24
Overseas:										
Europe	(15)	0.34	.....	0	(1)	0.37	(4)	0.24	(10)	0.42
Pacific	(19)	.61	(2)	.90	(1)	.21	(3)	.31	(13)	.92
Total overseas	*55*	*0.51*	*2*	*0.34*	*11*	*0.65*	*15*	*0.39*	*27*	*0.58*
Total Army	112	0.44	9	0.28	31	0.45	38	0.49	34	0.45

[1] Includes infectious encephalomyelitis and Japanese B type encephalitis as well as other types of infectious encephalitis. Excludes lymphocytic choriomeningitis.

[2] Includes postvaccinal encephalomyelitis.

[3] Data are not available.

[4] Includes encephalomyelitis, other and undetermined. Excludes lymphocytic choriomeningitis.

NOTE.—Figures in parentheses are subtotals.

No sizable epidemic due to one of the known encephalitic viruses was ever recorded in U.S. Forces stationed within the United States during the period 1942–45. However, a possible outbreak, of which the agent was never identified, occurred during the summer of 1941, when 12 mild cases of encephalitis developed in a force of unknown size maneuvering near Sabinal, Tex.[5] Sporadic cases of proved arthropodborne virus encephalitides occurred in western training areas during 1942–45, but the incidence never reached anything comparable to that experienced by the Canadian troops in Manitoba in 1941. Clinical descriptions of these sporadic cases in U.S. troops apparently did not differ from the usual textbook descriptions, and no unusual findings are known to the author.

Outside the confines of the United States, a single case due to one of the exotic South American types of the neurotropic viruses was recorded of a

[5] Woodland, J. C., and Smith, E. M.: Acute Encephalitis; Mild Epidemic Observed at Station Hospital, Fort Sam Houston, Texas. J.A.M.A. 120: 358–361, 3 Oct. 1942.

U.S. Navy seaman in Trinidad in 1943. It proved to be due to the virus of Venezuelan equine encephalitis.[6]

By far the most important group of cases, however, which occurred during the Second World War took place in an oversea theater. This was the small but important outbreak identified as Japanese B encephalitis which involved both natives and troops on the island of Okinawa in the summer of 1945.

In the spring of 1945 and at the time of the occupation of islands north and northwest of Guam, the Medical Department recognized that U.S. troops were entering territory where Japanese B encephalitis might be endemic. For this reason, knowledge of the disease was summarized for use by medical officers in War Department Technical Bulletin (TB MED) 181, July 1945. Japanese B encephalitis had been previously reported as recurring not only in Japan proper but in the Ryukyu Islands, Formosa, Korea, eastern China, in certain of the far eastern maritime districts of the U.S.S.R., and in Manchuria. However, it was uncertain whether the Japanese B virus was the sole etiological agent of encephalitis within all these areas.

The epidemic occurred during a combat period on the island of Okinawa and has been well described by Sabin,[7] so that his account need not be repeated here. It may suffice to say that the occupation of Okinawa, representing, as it did, a very strategic area, had been achieved in April 1945, and during the entire spring and early summer months, fighting continued sporadically on the island. Encephalitis first appeared among the native population early in July. The first native patients with severe encephalitis observed by American medical officers in the Ryukyus were seen by Lt. L. M. Miller, MC, USNR (of the local military government) on 8 July 1945 on Heanza Shima, a small island about 2 miles east of Okinawa. During the following 3 months, 127 patients were seen by military government medical facilities on the two islands; 66 of the 91 patients found on Okinawa were admitted to the isolation hospital for observation and treatment. The etiological agent of the disease was first established by the results of complement fixation and neutralization tests and by recovery of the virus from a fatal case.

Two groups of workers participated in these identifications. The civilian cases were first identified by Hodes, Thomas, and Peck,[8] of the Naval Medical Research Unit No. 2, then established on the island of Guam, and subsequently, military cases were identified by Lt. Col. Albert B. Sabin, MC,[9] member of the Commission on Neurotropic Virus Diseases, Army Epidemiological Board. This achievement by American medical officers in recognizing clinically and,

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[6] Randall, R., and Mills, J. W.: Fatal Encephalitis in Man Due To Venezuelan Virus of Equine Encephalomyelitis in Trinidad. Science 99: 225-226, 17 Mar. 1944.

[7] (1) Sabin, A. B.: Epidemic Encephalitis in Military Personnel; Isolation of Japanese B Virus on Okinawa in 1945; Serologic Diagnosis, Clinical Manifestations, Epidemiologic Aspects and Use of Mouse Brain Vaccine. J.A.M.A. 133: 281–293, 1 Feb. 1947. (2) See footnote 3, p. 83.

[8] Hodes, H. L., Thomas, L., and Peck, J. L.: Cause of an Outbreak of Encephalitis Established by Means of Complement-Fixation Tests. Proc. Soc. Exper. Biol. & Med. 60: 220–225, November 1945.

[9] Sabin, A. B.: Outbreak of Encephalitis on Okinawa in 1945: Preliminary Report on Status as of August 27, 1945. J. Mil. Med. in Pacific 1: 79-84, November 1945.

subsequently, in identifying the etiology of Japanese B encephalitis was accomplished under arduous combat conditions and was indeed a noteworthy event, both in military medicine and in the history of this disease in general. At the time the disease was discovered, the island was the most important advanced base in the Pacific area. Large forces of U.S. troops were already assembled for the projected invasion of the home islands of Japan scheduled for the autumn. It was reasonable to assume that these troops were and would be susceptible to neurotropic virus disease to which they had never been previously exposed, and the danger of an epidemic was therefore a matter of great concern to the Medical Departments of the Army and the Navy. The news of the epidemic of "a dread Japanese brain disease" on Okinawa had also spread among the troops with demoralizing effect.

It is hard today to appreciate the difficulties which confronted medical officers at that time, but the story of these difficulties has been well documented by Lt. Col. William D. Tigertt, MC, and Dr. Hammon.[10] They pointed out that in 1945, available information about the presence of the disease on Okinawa was meager. Although Japanese B encephalitis had been stated to occur on Okinawa, the figures were difficult to assess since cases of epidemic cerebrospinal meningitis, encephalitis lethargica, and malaria with cerebral symptoms were also reported, usually with the diagnosis made on clinical grounds. Furthermore, relatively few Japanese physicians had practiced on the island of Okinawa before World War II, and public health reports were fragmentary and incomplete there. Only later did it become known that Iimura had reported 68 cases of Japanese B encephalitis on Okinawa in 1933 (cited by Tigertt and Hammon) and that, in 1937, Takagi and others (cited by Tigertt and Hammon) had shown that most of the human sera collected on Okinawa contained neutralizing antibodies.

Mosher[11] has described how the situation was handled on Okinawa in July and August 1945. The investigation of encephalitis was assigned to the Military Government Research Center, and on 18 July 1945, an isolation hospital for the study of the disease was opened at Gimbaru. By direction of the commandant of the U.S. Military Government, all native patients with cerebrospinal symptoms suggestive of encephalitis were referred to the research center from all parts of the island by field dispensaries, hospitals, and other medical units established to care for the natives. Dispensary personnel were instructed in the recognition of the disease, and in some areas native police assisted in finding the sick. A visiting nurse program was instituted by some of the dispensaries. While these nurses were largely untrained volunteers, they facilitated in some degree in case finding and in referral of cases to the hospitals. Between early July and October, a total of 91 natives of Okinawa

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[10] Tigertt, W. D., and Hammon, W. McD.: Japanese B Encephalitis: A Complete Review of Experience on Okinawa, 1945–1949. Am. J. Trop. Med. 30: 689–722, September 1950.

[11] Mosher, W. E., Jr.: Japanese "B" Encephalitis; Epidemiological Report of the 1945 Outbreak on Okinawa. U.S. Nav. M. Bull. 47: 586–593, July-August 1947.

were diagnosed as having encephalitis, the morbidity being 2.8 per 10,000, as compared with 44.7 for the Heanza-Hamahika Islands.

Among U.S. military personnel, between July and mid-September, 38 military patients exhibited a variety of clinical manifestations and were investigated by serological methods for the diagnosis of Japanese B encephalitis. Of these, only 11 yielded unequivocal evidence of the specific infection. Two of the eleven died, and autopsy revealed cerebral lesions compatible with the diagnosis of viral encephalitis. It is highly probable that more than 11 cases occurred.

In a report of the outbreak by Lewis and his associates,[12] which represents perhaps the first extensive clinical description of Japanese encephalitis made by U.S. physicians, the symptomatology of the disease was described as it occurred among Okinawan natives. The clinical features of the cases in U.S. military personnel, as observed both on Okinawa and subsequently in Korea, have been well documented in War Department Technical Bulletin (TB MED) 181 on Japanese B encephalitis, issued on 6 April 1947.

Although the clinical features of Japanese B encephalitis do not seem to differ materially from those of St. Louis encephalitis and western equine encephalomyelitis, which were already in 1945 well described in U.S. textbooks of medicine, it may be worthwhile to mention something here of the clinical picture of Japanese encephalitis as it appeared on Okinawa. Most important for diagnostic purposes was the appearance of the following signs during the course of an acute febrile illness: Mental confusion, disorientation, purposeless movements, speech disturbances, and complete aphasia. Varying degrees of lethargy might be present ranging from abnormal somnolence to complete coma in patients who also exhibited high fever and nuchal and spinal rigidity. As a rule, there was a period of 2 or 3 days before the appearance of any signs suggesting involvement of the nervous system. During this time, headache and low-grade fever were the only symptoms. Generalized convulsions of the grand mal or petit mal type were occasionally the first signs of involvement of the nervous system, with stiffness of the neck and back, and other signs already mentioned, coming later. Flaccid paralysis, suggesting involvement of large numbers of lower motor neurons in the spinal cord or medulla, was not seen. Localized spastic paralysis was seen only once among 15 patients, although generalized rigidity was present in the more severe cases. Dissociated eye movements were seen in only one patient, and diplopia did not occur. Pupils were usually contracted and reacted poorly to light; a sticky exudate was not infrequently seen about the eyes. The reflexes were variable and by themselves of little aid in differential diagnosis. The abdominal reflexes were usually absent while the tendon reflexes were most exaggerated; only occasionally did they become diminished or absent. Babinski's sign was rarely elicited.

[12] Lewis, L., Taylor, H. G., Sorem, M. B., Norcross, J. W., and Kindsvatter, V. H.: Japanese B Encephalitis; Clinical Observations in an Outbreak on Okinawa-shima. Arch. Neurol. & Psychiat. 57: 430-463, April 1947.

As a rule, the fever lasted from 7 to 11 days. It was high after the appearance of nervous signs and frequently remittent, although it is uncertain to what extent the administration of antipyretics may have affected the temperature curve. A relative bradycardia was invariably present during the febrile phase with a pulse rate of about 50 to 60 being common after defervescence. In fatal cases, death due to encephalitis occurred within the first 2 weeks and, as a rule, during the first 7 days after onset.

Convalescence was slow. Lethargy and incoordination, tremors and nervousness, and occasionally distinct personality changes persisted for some weeks after defervescence. Subsequently, it became apparent from observations by Japanese physicians and by neurological consultants from the United States that residual symptoms from this disease were noted in only a small percentage of patients.[13] These did not grow progressively worse as in the sequelae in encephalitis lethargica.

As to laboratory findings in the blood and spinal fluid, during the acute phase of the disease, the white blood cells in the former were likely to be increased in the range of 10,000 to 25,000 cells per cubic millimeter of blood, with a definite increase in the number of mature and immature neutrophiles. Cerebrospinal fluid was clear, under normal or occasionally increased pressure, and pleocytosis, ranging from 22 to 1,450 white blood cells, was present in all of the military patients whose illness was definitely proved to be due to this infection. The cells were, as a rule, predominantly mononuclear, although in at least two of the group polymorphonuclear leukocytes predominated; spinal fluid sugar and chloride were in the normal range. Protein was normal or only slightly increased early in the disease, while during convalescence a 3 or 4 plus Pandy reaction was not uncommon.

In American military personnel, poliomyelitis and "aseptic meningitis" [14] offered the greatest problems of clinical differential diagnosis. Among the children and natives of older age groups, tuberculous meningitis proved to be another important differential diagnostic consideration. Of aid in the diagnosis was the use of neutralization and complement fixation tests and virus isolation from fatal cases. It was fortunate indeed that, during the

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[13] During World War II, and when this disease was first encountered, a subject of great interest was whether the military cases of Japanese B encephalitis would result in any residual deficiencies in nervous function after the acute stage of the disease had been passed successfully. This was a matter which should call for preferably long-term followup observations. One postwar study which can be mentioned is embodied in a report to the Surgeon General's Office by Dr. Charles D. Aring, Professor of Neurology, University of Cincinnati, Ohio, made under the auspices of the Army Epidemiological Board in 1948 (published in Arch. Neurol. & Psychiat. 62: 759–765, December 1949). Dr. Aring examined 19 late cases of Japanese B encephalitis in Americans at the 361st Station Hospital in Tokyo, as well as 12 late cases among Japanese. In only 1 American out of a total of 19 did he feel that it was possible that the patient was suffering from residua, and even in this case it seemed probable that the signs were attributable to an emotional disorder apart from his recent acute disease. It was Dr. Aring's opinion that once the "dangerous period" had been passed without the appearance of crippling neurological signs, the patient would go on to good recovery, with the possible exception of the development of parkinsonism, which had been reported in Japanese cases as an occasional occurrence.

[14] Several years later, it was shown that leptospirosis was the cause of at least one outbreak of "aseptic meningitis" in troops on the island of Okinawa.

combat conditions on Okinawa in the summer of 1945, not only were laboratory facilities made available for the carrying out of these tasks but that personnel were also available to do the tests and to interpret them. This is a type of frontline scientific medicine which deserves special mention in any military history.

Medical officers were aware that there was no specific treatment for Japanese B encephalitis, but the following supportive measures were carried out. During the period of coma, nutrition was maintained by gavage or by the parenteral administration of fluids and the use of vitamin supplements. As depletion of body protein was sometimes extreme, plasma or amino acids were given.

Other special and general methods were used as a means of preventing decubitus ulceration. The careful use of sedatives during periods of restlessness and irritability, with frequent changes of posture of comatose patients, tracheal aspiration, catheterization when indicated, and similar routine procedures constituted almost all the therapeutic measures.

The treatment of complications with chemotherapeutic agents was regarded as of paramount importance, particularly with reference to pneumonia.

The pathology of Japanese B encephalitis was also described on the basis of material studied from the Okinawan epidemic. An excellent report was made by Lt. Comdr. H. M. Zimmerman, MC, USNR, from the Naval Medical Research Unit No. 2 [15] and, with the help of the Army Institute of Pathology (now the Armed Forces Institute of Pathology), Washington, D.C., another report was made by Haymaker and Sabin.[16] Involvement of the brain proved to be very extensive.

For preventive measures, the reader is referred to Sabin's chapter on encephalitis in another volume in the history of the Medical Department in World War II.[17] It is enough to say here that the use of mosquito control and a mouse-brain formalin (inactivated) vaccine were tried on Okinawa.

In summary, therefore, and in retrospect, it would appear that during World War II after considerable preparation with regard to the arthropodborne virus encephalitides this group of diseases turned out to be less of a threat as a military disease than had been anticipated, but in this respect there was feeling that the Armed Forces had been lucky. In any event, considerable was learned about arthropodborne virus encephalitides which constituted a group of what might be called new diseases as far as the Medical Departments of either the Army or the Navy were concerned. The first contact by American troops with a most important member of this group, namely, Japanese B encephalitis, became a landmark of some prominence

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[15] Zimmerman, H. M.: The Pathology of Japanese B Encephalitis. Am. J. Path. 22: 965-991, September 1946.

[16] Haymaker, W., and Sabin, A. B.: The Topographic Distribution of Lesions in Central Nervous System in Japanese B Encephalitis; Nature of the Lesions, With Report of a Case on Okinawa. Arch. Neurol. & Psychiat. 57: 673-692, June 1947.

[17] See footnote 3, p. 83.

in the military history of virus diseases. That the disease should have been promptly recognized, and the agent isolated by medical officers from the Army and the Navy working close to the combat areas, was a noteworthy achievement. Subsequent to World War II, important additions were made to knowledge about this disease, as a result of experiences in the army of occupation in Japan,[18] but the introduction to this story came in July and August of 1945 on the island of Okinawa.

POLIOMYELITIS

Just prior to the onset of World War II, it was generally agreed by medical officers in the Army that poliomyelitis was not a disease of military significance. This was based on the very low incidence of poliomyelitis in U.S. Army forces during and in the years immediately following World War I. It seemed justifiable to continue to regard this disease essentially, if not exclusively, as a disease of early childhood and not, to any appreciable degree, as a disease of men of military age.

By 1945, however, it was abundantly clear that this opinion needed revision, for although the number of cases of poliomyelitis which had occurred in the Army during World War II was not very great (in the neighborhood of about 1,000 covering the 4 war years), the disease had been responsible for many problems. The degree of crippling was high; the percentage of bulbar cases was high; the mortality was high; and the element of panic which poliomyelitis caused, either in outbreaks or in single cases within military units, had proved to be appreciable. Not only had this been so within the confines of the United States but, with the exception of the European Theater of Operations, U.S. Army, the incidence of poliomyelitis had been considerably greater in troops abroad than at home (p. 99).

The statistics with regard to the prevalence of poliomyelitis in U.S. Army personnel preceding and during World War II have been admirably

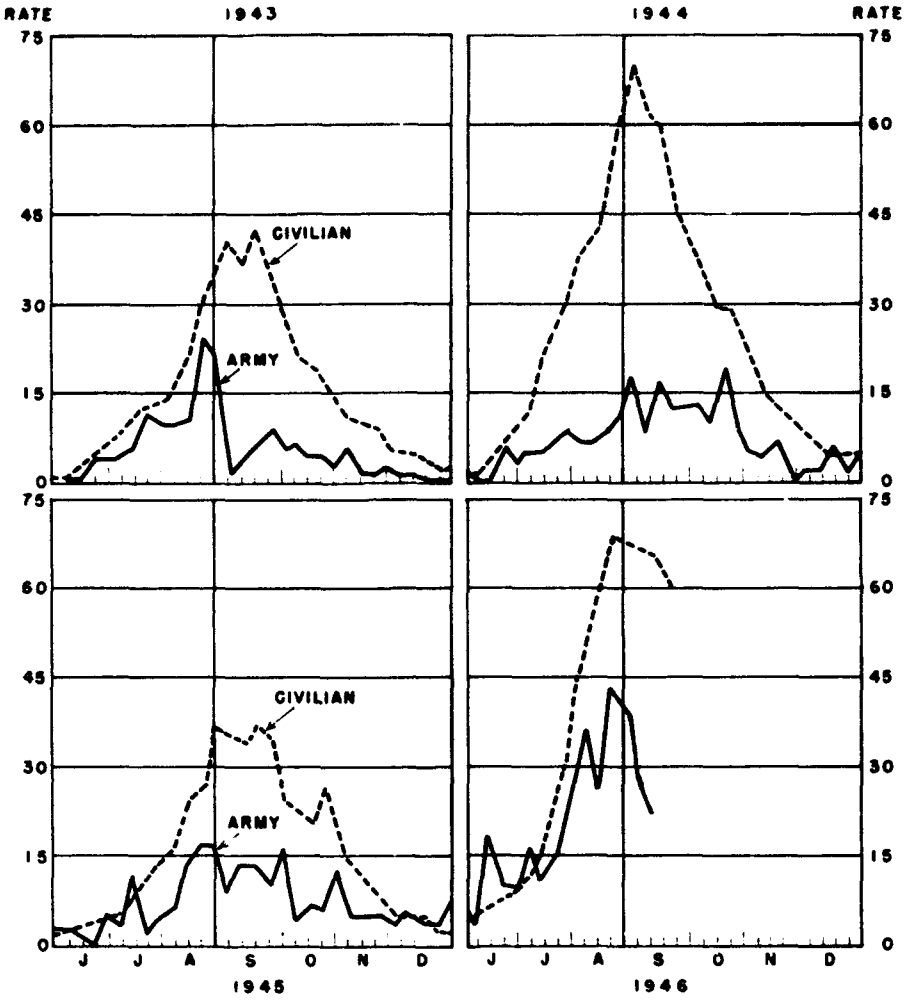
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[18] It will not be within the scope of this chapter to discuss postwar outbreaks of arthropodborne virus encephalitis or the experience with this disease by troops occupying Japan during the 2 years immediately following 1945. Three cases did occur in U.S. troops in Korea in 1946, one of them fatal. These occurred among 1,500 Americans stationed in an isolated camp near Kunsan (Sabin, A. B., Schlesinger, R. W., Ginder, D. R., and Matumoto, M.: Japanese B Encephalitis in American Soldiers in Korea. Am. J. Hyg. 46: 356–375, November 1947). No cases of encephalitis were found in the native population coincidentally. Subsequently (1946–55), Korea has experienced at least two large outbreaks of Japanese B encephalitis.

Also during the summer of 1946, an outbreak of illness among U.S. Marines stationed in Tientsin, China, which at first was thought to be encephalitis and later regarded as poliomyelitis, led to certain investigations by Sabin and his coworkers (Proc. Soc. Exper. Biol. & Med. 65: 183–187, June 1947) which revealed that extensive previous inapparent infection with Japanese B encephalitis virus existed among the populations of Shanghai and Tientsin, where no epidemics of encephalitis had been observed. The survey method employed by Sabin was one which had been followed by Japanese in Japan and elsewhere, for some years; namely, by determining the presence or absence of neutralizing antibodies for the virus of Japanese B encephalitis in large numbers of sera collected from various age groups of the local population living in various locations. It was, however, one of the first of many subsequent examples of the use of the serological antibody survey by U.S. investigators as a means of outlining the geographic distribution of epidemic encephalitis in what might be called unknown territory.

CHART 2.—*Seasonal incidence of poliomyelitis in the Army in the continental United States compared with contemporaneous civilian rates during the second half of each year, 1943–46*

[Rate expressed as number of cases per annum per 100,000 average strength, by weeks]



Source: Health of the Army, vol. I, Report No. 3, 30 Sept. 1946.

reviewed by Sabin in another volume in the history of the Medical Department in World War II.[19] The attempt will not be made, therefore, to duplicate Sabin's figures to which the reader may be referred. There are, however, certain epidemiological points which deserve mention even at the expense of reiteration because they represent new information about this disease acquired as a result of military experience. Primarily, it became apparent during the years 1941–45 that men of military age, born and brought up in the United States during the 1920's and 1930's, were more susceptible to poliomyelitis than their fathers had been in 1917–18. This was unexpected. The military rates for 1943–46 within the United States

[19] Sabin, Albert B.: Poliomyelitis. *In* Medical Department, United States Army. Preventive Medicine in World War II. Volume V. Communicable Diseases Transmitted Through Contact or By Unknown Means. Washington: U.S. Government Printing Office, 1960, pp. 367-400.

are shown in chart 2. In comparing the curves recording Army and civilian incidence, respectively, in chart 2, one should recall that the civilian population contains a much higher percentage of susceptibles (children) than does the military population In terms of actual rates, the average civilian overall annual rate for poliomyelitis per 100,000 in the United States for 1940–47 was about 10. This includes all ages, all months of the year, and both paralytic and nonparalytic cases. It can be compared with the annual rate for U.S. Army troops in the United States for the period 1940–47, which was about 3 per 100,000.

Another point that came out of the military experience was that in 1941 there was little appreciation that poliomyelitis could be a tropical disease of any importance, or that it amounted to much in subtropical areas. Local civilian public health statistics within the great majority of tropical areas had for years reported a dearth of epidemics and a very low incidence of poliomyelitis in the native-born inhabitants.[20] Therefore, it was naturally thought that this disease should not be of particular danger to troops in such areas. It was not long, however, before it became apparent that poliomyelitis could exist in poorly sanitated tropical or subtropical areas as a hidden disease, hitherto unsuspected. Later, by the copious use of hindsight, one could surmise that this might have been predicted on the basis of prewar experience with poliomyelitis in the Philippines. As early as 1936, Lt. Col. (later Brig. Gen.) Charles C. Hillman, MC, had reported an interesting observation, which was to be repeated frequently during World War II. In his account [21] of an outbreak of poliomyelitis which occurred in Manila, Philippine Islands, in 1934, he described 17 patients with poliomyelitis who were admitted to the Sternberg General Hospital in Manila; of these, 3 cases were in military personnel, the remaining 14 being in dependents. Coincidentally, the number of cases in the local Philippine civilian population was small, presumably represented by only nine cases. Colonel Hillman commented on the fact that, considering the vast preponderance of natives to American-born people in the community, there was indeed a striking discrepancy between the poliomyelitis incidence rate in the civilian population and that of the Americans. However, the extraordinary degree to which the immunity of the young adults in the two populations might differ was not appreciated at that time.

The idea should not be conveyed here that the Medical Department of the U.S. Army was indifferent at the beginning of World War II to the threat of poliomyelitis as a possible problem in military medicine, for this was not the case. During the summer of 1941, the Office of the Surgeon General of the Army prepared a statement about poliomyelitis and recommendations for its control in the Army. Again in 1943, at the request of

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[20] Since 1945, many epidemics of poliomyelitis have been reported from tropical areas (Paul, J. R., Ramirez Corria, F., and Horstmann, D. M.: Analyses From a Tropical Epidemic of Poliomyelitis Which Occurred in Florida and Cuba in 1946. Am. J. Trop. Med. 29: 543–554, July 1949).

[21] Hillman, C. C.: Poliomyelitis in the Philippine Islands. Mil. Surgeon 79: 48–58, July 1936.

The Surgeon General of the Army, the Division of Medical Sciences of the National Research Council sponsored a discussion by outstanding authorities in the field of poliomyelitis, which again resulted in a number of recommendations used by military officers. These recommendations are recorded by Sabin in another volume in the history of the Medical Department in World War II.[22]

Perhaps the first theater in which this disease became an appreciable problem was that of the U.S. Army Forces in the Middle East in 1943. Observations regarding the seriousness of poliomyelitis in British troops within the area during 1941–42 had already been made in 1943.[23] The situation was later reviewed by Caughey and Porteous in a postwar report of their experiences which includes a description of an epidemic of poliomyelitis which had occurred in 1940–41 in New Zealand troops stationed in Egypt.[24] Similar British observations were recorded in India with comments on the fact that poliomyelitis was particularly severe in foreign troops in India, whereas at the same time it seemed to be both uncommon and not severe in the natives there.

This early British experience in the Middle East was later shared by U.S. troops in North Africa, Egypt, and the Middle East generally during the summer of 1943. This joint experience has been described[25] with particular reference to the high rate and high fatality of poliomyelitis in U.S. troops in contrast to its apparent rarity in the native adult Egyptians. Comment was also made on the absence of epidemics of poliomyelitis in the local native population and the fact that the only examples of the disease which did appear in the local population were in infants.

There was considerable difficulty with the diagnosis of poliomyelitis in U.S. troops stationed in this area during the summer of 1943. Medical officers had not been prepared for this disease and were very loath to accept suspicious cases as poliomyelitis. This may be understandable in that, at least at that period, the clinical picture of poliomyelitis in adults had received scanty treatment in American textbooks of medicine. At the 38th General Hospital near Cairo, Egypt, this author, in consultation, saw at least a dozen cases of poliomyelitis, several of which were fatal. In the majority of patients, the disease was characterized by insidious onset with 2 or 3 days of malaise, relatively little fever, but severe pain in the back. This is in some contrast to the textbook picture seen in children with an acute onset with fever and usually a biphasic course. Fortunately, at the 38th General Hospital, a virus laboratory had been established in the sum-

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[22] See footnote 19, p. 92.

[23] Van Rooyen, C. E., and Morgan, A. D.: Poliomyelitis; Experimental Work in Egypt. Edinburgh M.J. 50: 705–720, December 1943.

[24] Caughey, J. E., and Porteous, W. M.: An Epidemic of Poliomyelitis Occurring Among Troops in the Middle East. M.J. Australia 1: 5–10, 5 Jan. 1946.

[25] Paul, J. R., Havens, W. P., Jr., and Van Rooyen, C. E.: Poliomyelitis in British and American Troops in the Middle East; Isolation of the Virus from Human Faeces. Brit. M.J. 1: 841–843, 24 June 1944.

mer of 1943. Monkeys were obtained locally and from Eritrea, where they had been trapped by members of the Army Veterinary Service, and the isolation of poliomyelitis virus by monkey inoculation with material from a number of these cases during the summer of 1943 supported the diagnosis.[26]

In the care of these patients, there is little to record other than the fact that here, as elsewhere in areas remote from the United States, tank respirators and other respiratory aids were seldom available. As a result, poliomyelitis patients who developed severe respiratory paralysis promptly died.

From the epidemiological standpoint, it was here in the Middle East that the idea first emerged that the phenomena which had been observed by Hillman in the Philippines in 1934 was one which could be repeated in a number of different areas, particularly in cities located in the tropics where sanitation was primitive. In other words, among the native-born infants and young children in these areas, poliomyelitis was apt to be endemic with an exposure rate so high that the infection was almost universally acquired by natives in infancy and was almost universally unrecognized. Consequently, by the time the native child had reached the age of 2 or 3 years, he had had the disease (rarely in either paralytic or nonparalytic form), but commonly in inapparent form and had thus acquired some immunity. This immunity rate among the adult natives was high as opposed to the visiting troops from northern Europe, the United States, Canada, Australia, and New Zealand whose exposure to poliomyelitis at home had not been so heavy during infancy. When these troops entered these areas, poliomyelitis came to the surface, as it were, because of heavy exposure of a moderately susceptible population coming into an infectious environment. As a result, not only were appreciable numbers of cases of poliomyelitis acquired by the susceptible members of the "immigrant" troops, but small epidemics in U.S. troops were precipitated now and again of which notable examples appeared in 1944 and 1945 in the Philippines.

It would also appear that the same unsanitary conditions and proximity to native populations, which gave rise to high attack rates of bacillary dysentery and infectious hepatitis, were also associated with an increased incidence of poliomyelitis. Thus, poliomyelitis and these other diseases did not often occur among the troops in various primitive, tropical or subtropical, regions where the military installations were "beyond the range and influence of native villages." But where, as became particularly evident in the Southwest Pacific Area and in the Philippines, U.S. troops moved into the midst of congested native villages and towns with sanitation of the worst possible order, poliomyelitis appeared in unexpectedly high numbers of cases, along with the other infections whose etiological agents were known to occur predominantly in human feces.

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[26] Report, Commission on Neurotropic Virus Diseases, Army Epidemiological Board, to Office of the Surgeon General, U.S. Army, May 1944, subject: Report of the Middle East Expedition of the Virus Commission.

In the Philippine Islands, for instance, the story was typical. Prior to the invasion of the islands in 1944, the attacking force had spent a month on board ships without the appearance of a single case of poliomyelitis. But shortly after the occupation of Leyte began in October 1944, cases appeared, and this was followed by a relatively high incidence of the disease. According to the statistical health report, 39 cases of poliomyelitis occurred, during the months of November and December 1944, in a force which varied from an initial strength of about 200,000 to a little over 300,000 at the end of the year. In the next year, there were 245 cases (for all of 1945) in a force with an average strength of around 600,000. Sabin states that there is good reason to believe that this does not include all the cases. Studies on the disease here were reported by the virus team of the 19th Medical General Laboratory, Leyte.[27] It was noted by them that there was no uniform history of the increase of upper respiratory infections in units involved, but several of the patients had had diarrhea or dysentery subsequent to arrival on Leyte. Nonparalytic cases were also recorded; several of them caused considerable difficulty in diagnosis. Coincidentally, no evidence of poliomyelitis appeared among the Filipinos so that in the Philippine Islands poliomyelitis was considered to be a disease of white people. In retrospect, the observations point to the fact that the local population in Leyte was the hidden reservoir of the virus.

Another outbreak in the Southwest Pacific was investigated at Laoag Army Air Base in 1945 by Lt. Col. Adam J. French, MC.[28] Twenty-two cases occurred, most of them during the month of May, with at least eight paralytic cases. Here again, it was not an isolated explosive outbreak but rather a group of cases resulting from what seemed to be continuous exposure to a reservoir of virus.

Apart from the incidence of poliomyelitis in various oversea theaters, the incidence of poliomyelitis in troops in the continental United States was appreciable (chart 2). As a rule, most of the cases were sporadic examples of the disease which were not followed by outbreaks in the units in which they appeared. However, there were several small, sharp, and moderately serious epidemics in the United States during the period 1941–46. These epidemics have been discussed with care by Sabin in another volume in the history of the Medical Department in World War II.[29]

The first of these was an epidemic in San Antonio, Tex., in December 1942.[30] Although only 3 cases, 1 of them fatal, occurred in soldiers in the vicinity of Fort Sam Houston, San Antonio, there were a number of cases

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[27] Report, 19th Medical Service Detachment (General Laboratory), to Chief Surgeon, Headquarters, U.S. Army Services of Supply, Southwest Pacific Area, 28 Dec. 1944, subject: Poliomyelitis and Other Virus Diseases in the Tacloban-Palo-Dulag area of Leyte.

[28] Letter, Lt. Col. A. J. French, MC, to Chief Surgeon, U.S. Army Forces, Western Pacific, 25 June 1945, subject: Investigation of Poliomyelitis Outbreak at Laoag Army Air Base.

[29] See footnote 19, p. 92.

[30] Paul, J. R.: Preliminary Report on the Poliomyelitis Epidemic in San Antonio, Tex., September-December 1942. [Official record.]

among the families of officers and men stationed in that area, 11 of which were admitted to the Brooke General Hospital at Fort Sam Houston. This outbreak caused considerable concern locally and served as an illustration of the manner in which poliomyelitis can indirectly become a morale problem when it suddenly appears in the families of military personnel living on a large military post in this country.

A second outbreak, which was well described, occurred in a training unit designated as the STAR (Specialized Training and Reassignment) unit at Pasadena College, Pasadena, Calif. The STAR unit consisted of approximately 800 men among whom an explosive epidemic occurred in mid-August 1943, just after 310 of the men had left for duty at Indiana University, Bloomington, Ind. The first case, which ended fatally, occurred on the train, and subsequently, there were 16 other cases compatible with the diagnosis of paralytic or nonparalytic poliomyelitis in the group which went to Indiana. Among the men remaining at Pasadena College, there was only one case.

Another epidemic occurred at Fort McClellan, Ala., in the spring of 1945, which was apparently the only example of an outbreak of poliomyelitis in an isolated Army camp in the continental United States. Seventeen cases of paralytic poliomyelitis occurred within a brief period of 2 months, yielding a paralytic attack rate of approximately 0.57 per 1,000 men. All the cases were in soldiers.

These last two small outbreaks which occurred in Army personnel in the United States were both explosive localized types, suggesting primary infection from a common source over a limited period of time.

The incidence of poliomyelitis among American troops in the European theater was of the same order of magnitude as in the United States, except that no outbreaks were recorded.

Diagnosis

During World War II, poliomyelitis proved to be a disease of some significance within several theaters. This had been more or less unsuspected by medical officers, some of whom went to considerable lengths to determine whether the case of acute paralysis seen in North Africa, for instance, in 1943, might be due to some cause other than poliovirus. One of the reasons for the difficulties in making the diagnosis seemed to have been that at that time, in the mid-1940's, the average medical or pediatric textbook description of acute poliomyelitis described the picture of the juvenile case characterized with initial signs and symptoms of acute fever (often in two bouts), headache, vomiting, and stiff neck. Textbook descriptions of adult cases were few, and there was little awareness that adult cases could present a picture, quite different from the juvenile case, of insidious onset, often with little fever in the first few days and often with severe pain in the back. Consequently, it was with some reluctance that the diag-

nosis of poliomyelitis was made by medical officers in areas where poliomyelitis was said to be rare and where there was the possibility of the occurrence of one or more unusual diseases of local origin which might simulate poliomyelitis. This reluctance to diagnose poliomyelitis, because it was a disease that was not supposed to occur in certain parts of the world and not supposed to occur in soldiers, is understandable. By early 1944, cases of poliomyelitis in military personnel were becoming more familiar in the Mediterranean area, and the diagnostic problems were soon resolved.

Treatment

It would not be profitable to review the various kinds of treatment which patients with paralytic poliomyelitis received under widely differing circumstances in different theaters of war and in different kinds of hospitals. During and immediately following World War II, current ideas as to the symptomatic and supportive therapy of poliomyelitis were undergoing certain changes. The abandonment of the prolonged and rigid splinting of paralyzed limbs was taking place, and the tendency was more in favor of the use of shell casts to protect the weakened or paralyzed limb rather than its fixation. Actually, the degree to which rigid splinting of paralyzed limbs during acute phases of the disease was carried out must have differed considerably in different places. Another innovation was just beginning to be used. This was the application of moist heat to the limbs and body in the painful stages of myelitis, the so-called Sister Kenny method, which also called for the reeducation of muscles early in the postfebrile period.

Considerable improvements were to be made in the decade following World War II in the development of various mechanical breathing aids for supporting patients whose life was threatened because of respiratory impairment as a result of paralysis to the respiratory muscles. During World War II, however, the main respiratory aid was the tank respirator, known as the Drinker respirator. This was a large, heavy piece of apparatus, bulky and difficult to transport. It was not standard equipment of many general hospitals. Nevertheless, a number of these tank respirators were available for hospitals in the United States, and occasionally, the emergency transportation of a tank respirator to a distant area was achieved. In retrospect and taking all things into account, it is not believed that loss of life due to the failure of availability of respiratory aids was a serious situation.

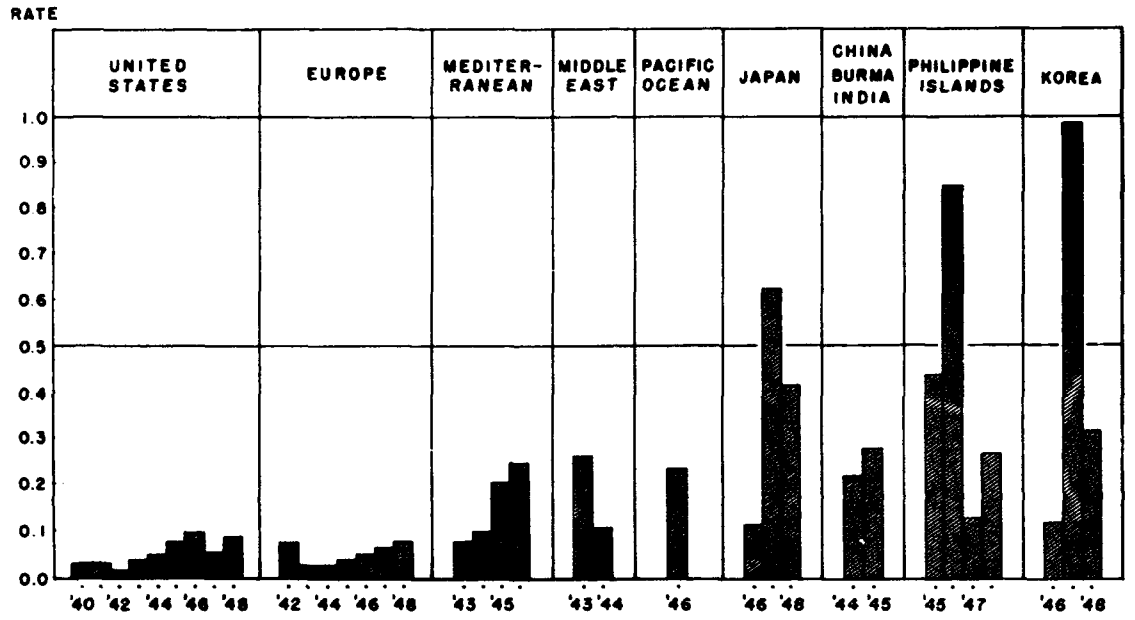
Oversea patients with residual paralysis were eventually evacuated to hospitals in the Zone of Interior where they could have orthopedic supervision and undergo a regimen of rehabilitation before discharge from the Army. This latter phase represents a different but important chapter in the handling of these cases.

In summary, therefore, it can be said that, before the close of World War II, it had become apparent that, with the exception of northern Europe,

the rates of poliomyelitis for U.S. troops stationed abroad were higher than in the United States, and in some instances far higher (chart 3). In this chart, the rates are indicated at which poliomyelitis appeared in U.S. Army troops, which were low in the United States and the European theater, were higher in the Mediterranean, the Middle East, and China-Burma-India theaters, and higher still in the Philippine Islands.

CHART 3.—*Incidence of poliomyelitis in the U.S. Army, by selected area and year, 1940–48*

[Rate expressed as number of cases per annum per 1,000 average strength]



Source: Paul, J. R.: Poliomyelitis Attack Rates in American Troops, 1940–1948. Am. J. Hyg. 50: 57–62, July 1949.

Unexpectedly, therefore, this military experience has added a good deal of knowledge to the epidemiology of poliomyelitis in general[31] but relatively little to other aspects of this disease. This was because of the small number of cases and the insufficient volume of clinical material.

LYMPHOCYTIC CHORIOMENINGITIS

The story of this disease in World War II has been presented by Rasmussen and Smadel in another volume in the history of the Medical Department in World War II.[32] From their review, it appears that lymphocytic choriomeningitis, which had been a popular diagnosis during the late 1930's,

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[31] (1) Paul, J. R.: Poliomyelitis in Japan. Am. J. Hyg. 45: 206–218, March 1947. (2) Sabin, A. B.: Epidemiology of Poliomyelitis; Problems at Home and Among Armed Forces Abroad. J.A.M.A. 134: 749–756, 28 June 1947.

[32] Rasmussen, Aaron F., Jr., and Smadel, Joseph E.: Lymphocytic Choriomeningitis. *In* Medical Department, United States Army. Preventive Medicine in World War II. Volume V. Communicable Diseases Transmitted Through Contact or By Unknown Means. Washington: U.S. Government Printing Office, 1960, pp. 363–366.

proved to be a much less common disease among U.S. military personnel than had been originally suspected.

Early in the war, this disease, which will be referred to here as LCM, had been considered of sufficient importance to deserve detailed mention in Circular Letters Nos. 107 and 74, 21 October 1941 and 19 March 1943, respectively, pertaining to neurotropic virus diseases; later, these circulars were followed by TB MED 212, 16 January 1946. In all of these summaries, it was pointed out that exact diagnosis was desirable and that aids to the clinical diagnosis of LCM were available in the form of complement fixation tests, which could preferably be performed for diagnostic purposes on matched samples of sera.

These directives reflect the fact that the clinical diagnosis of LCM was being made all too freely in the early 1940's and that the term had become a catchall to embrace the majority of cases of acute aseptic or lymphocytic meningitis of undetermined etiology. This explains the report of admission to Army hospitals of 758 cases of LCM in which the diagnosis was based on clinical criteria alone during the period. However, from the laboratory studies, reported by Rasmussen and Smadel (in which only 31 of 276 suspected cases were proved to be caused by LCM), it appeared that only 1 in 10 of these 758 cases reported in the Army were actually caused by the virus of LCM, giving an estimated overall incidence of 76 cases during three of the war years, 1943–45.

The problem of differential diagnosis on clinical grounds in cases of aseptic meningitis was in the early 1940's, and still is, very appreciable, particularly as the list of diseases which were considered in differentiating LCM from lymphocytic meningitis in military personnel was long. It included mumps meningoencephalitis, nonparalytic poliomyelitis, central nervous system syphilis, tuberculous meningitis, acute encephalitis of a variety of causes, tetanus, brain abscess, rabies, lymphocytic meningitis associated with malaria, and infectious mononucleosis. At that time, the syndrome associated with infections by a number of Coxsackie and Echo viruses was not known, and it is highly probable that such cases were also included under the term "acute benign lymphocytic meningitis." Furthermore, the syndrome of acute, benign lymphocytic meningitis encountered in leptospirosis was also not appreciated, and it is reasonable to suppose that such cases occurred because of their subsequent detection in areas where troops were stationed during World War II.[33]

In brief, then, it appears that although many cases of LCM were diagnosed clinically during the war, actually this disease was uncommon. The introduction of serological methods and the notification of medical officers that such methods were available did much to clarify this situation. It is quite clear that in many theaters of operations it was difficult to have the

[33] Professional History of Internal Medicine in World War II, 1 Jan. 1940 to 1 Oct. 1945, The Panama Canal Dept., vol. I, pp. 162–171. [Official record.]

special type of laboratory determinations performed, such as the serological diagnostic methods described in Circular Letters Nos. 107 and 74, and TB MED 212.

Nevertheless, it was gradually brought home to medical officers, in this country at least, that here was a disease of which, if loosely diagnosed, one could find many examples, but if rigidly diagnosed, particularly with the use of the complement fixation test, 90 percent of the cases could be eliminated. The fact that these tests were more readily available to physicians in the Medical Department of the Army than to many physicians in civilian practice indicates that here was a situation with certain educational potentialities.

In retrospect, therefore, it would seem that LCM did not prove to be a disease of military importance in World War II. The number of proved cases were few and scattered and, apparently, there was nothing special or consistent about the circumstances under which they occurred. One noteworthy feature about LCM during World War II was, however, that through the laboratories of the Army Medical Department Professional Service Schools, Army Medical Center, Washington, D.C., and a few other special laboratories, this proved to be one of the first of the virus diseases of the central nervous system in which an exact etiological diagnosis could be established by serological methods. Others in the group soon followed.

RABIES

Rabies among military personnel during World War II was rare and sporadic. In the U.S. Army, 1941–45, seven rabies deaths were reported on individual medical records, five occurring in the United States and one each in Panama and the Philippine Islands. Of the five patients who died in the United States, one had contracted the disease in Italy but had not reported for treatment until after returning to the United States.

This author reviewed three case reports of patients who had contracted the disease in the United States—one at Jefferson Barracks, Mo., in December 1941; one in Washington, D.C., in November 1943; and one at Chanute Field, Ill., in January 1944. The first two cases were due to dogbites; the third, to the bite of a skunk.

In the three case reports reviewed, there were no special features with regard to the history, clinical course, and treatment. The incubation period in two of the patients, one of whom received a full course of antirabic inoculation, was from 3 to 6 months; whereas, in the third patient, who was bitten on the lip and who had received but three injections of vaccine, it was about 5 weeks. Once symptoms started, the course was rapidly downhill with death in 3 to 4 days. Initial symptoms included malaise, anxiety, and drowsiness. These were soon followed by nausea, pain in the shoulders, increasing stupor, rapidly developing flaccid paralysis, and pharyngeal and

laryngeal spasm. Paraldehyde and Avertin (tribromolthanol) were employed as sedatives.

Despite the farflung activities of the U.S. Army during the course of the war, the only areas other than the United States in which the disease was contracted were, as just mentioned, Panama, the Philippine Islands, and Italy. This is extraordinary from the standpoint of the exposure which might have existed in North Africa and in the Middle East generally, but is of course not remarkable for Great Britain and France in the European theater.

Col. John E. Gordon, MC,[34] in a report from the European theater, noted that it was a novel sensation in the experience of most American physicians to be able to look with complete equanimity on the occurrence of a dogbite. Rabies had been so long absent from Great Britain by reason of the stringent quarantine practiced in that country that no need existed for administration of antirabic vaccine after bites by dogs or other animals. The last rabies in Great Britain occurred at the time of World War I.

The rabies situation in France was almost as favorable, for apparently no definite cases of rabies had been detected in animals for some years, and no human had died from rabies in France for 16 years.

Rabies was, however, reported in Berlin, Germany, in 1945, and occasional infections among animals were recognized in northwestern European countries. Most American medical officers consequently returned to traditional practice in the management of dogbites sustained in these areas.

Rabies transmitted by bats was a disease known to the Army, but was of no military significance since it did not produce human cases. This bat-transmitted disease is the cause of paralysis in livestock, principally cattle. It made its first appearance in Trinidad, in 1925, where, for 11 years thereafter, focal outbreaks reoccurred in cattle, with about 1,000 cases occurring annually. The rigorous control measures which were brought to bear in Trinidad and Venezuela are described by Maj. Richard T. Gilyard, VC.[35]

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[34] Gordon, John E.: A History of Preventive Medicine in the European Theater of Operations, U.S. Army, 1941–45, vol. II, pt. III, p. 51. [Official record.]

[35] Gilyard, R. T.: Bat Transmitted Paralytic Rabies. Cornell Vet. 35: 195–209, July 1945.

CHAPTER V

Q Fever

Charles A. Ragan, Jr., M.D.

OCCURRENCE

Q fever first appeared among Allied troops in 1944 and 1945 when several sharp outbreaks occurred in the Mediterranean (formerly North African) Theater of Operations, U.S. Army.[1] That it was not identified immediately was doubtless related to the fact that this rickettsial disease had first been described in 1937,[2] and that, with the exception of laboratory infections,[3] the disease had been reported only from Queensland, Australia, as occurring naturally in human beings. The author was present as Chief, Medical Service, 15th Field Hospital in Italy, when some of the first military patients were seen, and it must be confessed that there was no realization at that time that an unusual situation was developing. In retrospect, it is of interest to reflect upon the interplay of serendipity, error (a single positive Weil-Felix reaction), and the presence of Maj. Frederick C. Robbins, MC, in Naples that led to the realization that we were dealing, not with common primary atypical pneumonia, but with Q fever, appearing naturally in a locality far distant from Queensland. Subsequently, the disease was recognized in southern Italy, Greece, and Panama. Since World War II, Q fever has been recognized in California.[4]

Apennines outbreaks.—The 15th Field Hospital was set up in December 1944 as a three-platoon unit acting as a medical evacuation unit behind the U.S. II Corps in the Apennines north of Florence. The hospital was studying the feasibility of early return to duty of patients with various psychosomatic problems related to combat fatigue. In addition to such patients, there were others with trenchfoot, infectious hepatitis, and primary atypical pneumonia.

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[1] Unless otherwise noted, the material presented in this chapter was taken mainly from a series of articles which appeared in the *American Journal of Hygiene,* volume 44, July 1946, pp. 1–182.

[2] (1) Derrick, E. H.: "Q" Fever, A New Fever Entity; Clinical Features, Diagnosis and Laboratory Investigation. M.J. Australia 2: 281–299, 21 Aug. 1937. (2) Burnet, F. M., and Freeman, M.: Experimental Studies on the Virus of "Q" Fever. M.J. Australia 2: 299–305, 21 Aug. 1937.

[3] (1) Cox, H. R.: A Filter-Passing Infectious Agent Isolated From Ticks. III. Description of Organism and Cultivation Experiments. Pub. Health Rep. 53: 2270–2276, 30 Dec. 1938. (2) Dyer, R. E.: A Filter-Passing Infectious Agent Isolated From Ticks. IV. Human Infection. Pub. Health Rep. 53: 2277–2282, 30 Dec. 1938. (3) Hornibrook, J. W., and Nelson, K. R.: An Institutional Outbreak of Pneumonitis. I. Epidemiological and Clinical Studies. Pub. Health Rep. 55: 1936–1944, 25 Oct. 1940. (4) Dyer, R. E., Topping, N. H., and Bengtson, I. A.: An Institutional Outbreak of Pneumonitis. II. Isolation and Identification of Causative Agent. Pub. Health Rep. 55: 1945–1954, 25 Oct. 1940. (5) Lillie, R. D., Perrin, T. L., and Armstrong, C.: An Institutional Outbreak of Pneumonitis. III. Histopathology in Man and Rhesus Monkeys in the Pneumonitis Due To the Virus of "Q" Fever. Pub. Health Rep. 56: 149–155, 24 Jan. 1941.

[4] Clark, W. H., Lennette, E. H., and Meiklejohn, G.: Q Fever in California. III. Aureomycin in the Therapy of Q fever. A.M.A. Arch. Int. Med. 87: 204–217, February 1951.

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Radiological facilities under the direction of Capt. Stanley M. Wyman, MC, were excellent.

In late February 1945, an officer from Headquarters Company, 339th Infantry, was admitted with high fever and general malaise without localizing symptoms, a picture suggesting the preicteric phase of infectious hepatitis. A roentgenogram of the chest at admission was interpreted as normal. A macular erythematous rash appeared transiently, and typhus was then considered in differential diagnosis, because several of the medical officers in the 15th Field Hospital had had duty in North Africa and had seen the disease in native populations. For this reason, a Weil-Felix test was done and was reported as positive in a significantly high titer from the 2d Medical Laboratory in Florence. Shortly thereafter, a second roentgenogram of the chest revealed an area of pneumonic consolidation, and a presumptive diagnosis of primary atypical pneumonia was made.

Within the next month, 32 additional members of Headquarters Company, 339th Infantry, were admitted with febrile illness, and 20 more patients from this unit were seen in other Fifth U.S. Army hospitals with similar symptoms. Major Robbins of the 15th Medical General Laboratory in Naples came to investigate the reported positive Weil-Felix reaction. From the blood of one of the patients with pneumonitis, a strain of rickettsia characterized as *Rickettsia burneti* was isolated by inoculation into guinea pigs and subsequent transfer to chick embryo yolk sac. This was established as the Henzerling strain. Sera were obtained from 28 patients during acute illness and convalescence, and convalescent samples were obtained from 25 other patients. Complement-fixing antibodies to the Henzerling strain were found in the sera of all 53 patients.

A second outbreak, originating in the same vicinity, was observed in April 1945 in the 3d Battalion, 362d Infantry, involving 267 patients of whom 80 were personally observed in the 15th Field Hospital. Sera of the acute disease and convalescence were obtained from 29 unselected cases, and a rising titer of complement-fixing antibodies to the Henzerling strain was demonstrated. The Paige strain of *R. burneti* was isolated from one patient in this group. In this epidemic, 70 percent of the patients not personally observed were reported as having atypical pneumonia or pneumonitis, and the remainder had diagnoses of fever of undetermined origin, infectious hepatitis without jaundice, or upper respiratory infection. Occasionally, no final diagnosis was made.

In a survey carried out by Major Robbins, Lt. Col. Ross L. Gauld, MC, and Capt. (later Maj.) Frank B. Warner, MC, several localities appear to be epidemiologically implicated in the high incidence of disease seen in these two outbreaks. Insects in the presumed areas of infection were numerous but no specific rickettsial vectors were discovered and the spraying of DDT (dichlorodiphenyltrichloroethane) did not modify the pattern of the outbreak in the 339th Infantry. An incubation period varying from 14 to

26 days, with a peak at 19 to 20 days, was suggested by this epidemic. No cases developed in medical personnel caring for these patients. It was noted that the implicated areas were dusty, but no attempt was made to recover the reckettsia from dust. Rickettsia was successfully recovered from dust in California by DeLay, Lennette, and DeOme in 1950.[5] High complement-fixing antibody titers to the Henzerling strain were found in a group of civilians from the epidemic area. Several other outbreaks, which were similar in their clinical and epidemiological features but not proved serologically, occurred in small units in northern Italy and Corsica. All outbreaks seemed to be related to dusty habitations.

Laboratory outbreaks.—In June, July, and August, 1945, a laboratory outbreak of 20 cases developed in the 15th Medical General Laboratory in Naples. This epidemic was well documented by Major Robbins and was shown to have originated in the room of the laboratory where the Henzerling and Paige strains were being studied in guinea pigs and embryonate hens' eggs. The Seale strain of *R. burneti* was isolated in this epidemic, and rickettsiae were isolated from 16 of the 20 patients as early as the second day of disease and as late as the eighth. Complement-fixing antibodies to the Henzerling strain of rickettsia were absent in sera taken before the 7th to the 13th day of disease but were present with later specimens. The peak of the antibody response was reached on about the 21st day with a tendency to diminish after the 30th day. The disease contracted in the laboratory appeared to be somewhat more severe than that seen in the field, possibly owing to a greater initial exposure to the infectious agent; however, four patients, proved to be harboring rickettsia and sick with fever and malaise, developed no roentgenologic evidence of pneumonia.

Outbreaks originating in Greece.—During the outbreaks north of Florence, it was learned that an epidemic of 40 cases of pneumonitis had appeared in one company of a battalion of British paratroopers who had come to Rome, Italy, from Athens, Greece, in January 1945. The outbreak appeared to have developed in Athens, and the men recalled exposure to dust in an abandoned silk mill used as a bivouac. Dr. J. Caminopétros of the Pasteur Institute in Athens had obtained from the blood of patients with "Balkan grippe" an agent producing a transmissible febrile disease in guinea pigs. Guinea pig blood was sent by him to the Commission on Acute Respiratory Diseases, Army Epidemiological Board (Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army), and from this, a rickettsia strain similar to *R. burneti* was isolated at the Commission laboratories at Fort Bragg, N.C. A laboratory outbreak caused by the "Balkan grippe" strain of Q fever occurred in the personnel in this laboratory before the rickettsia had been definitely characterized from the material sent from Greece. As was so often the case with these epidemics of

[5] DeLay, P. D., Lennette, E. H., and DeOme, K. B.: Q Fever in California. II. The Recovery of Coxiella Burneti from Naturally-Infected Air-Borne Dust. J. Immunol. 65: 211-220, August 1950.

Q fever, the diagnosis was made in retrospect. Convalescent serum obtained from 35 of the British paratroopers who had been sick in Athens and Rome and sera from 43 well soldiers of the same battalion were tested for agglutinating antibodies to the "Balkan grippe" strain at Fort Bragg. Significant elevations were found in 29 of the 35 recovered cases, while only 9 of 43 men who had not been ill showed a high titer. Presumably, therefore, the epidemic in British paratroopers represented an infection with the "Balkan grippe" strain contracted in Athens.

Outbreak in Zone of Interior.—An outbreak of Q fever was observed at Camp Patrick Henry, Va., in May and June 1945, after approximately 7,500 troops returning from southern Italy had disembarked. The disease was apparently confined to five squadrons of an air force group. Careful case finding in one squadron revealed 143 patients—an attack rate of 38 percent. Agglutinating antibodies to the "Balkan grippe" strain of *R. burneti* were found, as were complement-fixing antibodies to the Australian strain, but no organism was isolated. The outbreak seemed to be related to a particular bivouac area, at Grottaglie Air Base near Taranto in southern Italy. Again, no cases developed in medical personnel caring for these patients.

Other outbreaks.—A single case of pneumonia was studied in Panama from which a strain of rickettsia similar to *R. burneti* was isolated. The British Army in 1944 had observed in the Mediterranean area several sharply localized epidemics of "atypical pneumonia" characterized by a high attack rate—up to 50 percent of a unit. These may have represented Q fever, but no serological proof for this was obtained.

CLINICAL FEATURES

Mode of onset.—In northern Italy, the disease was characteristically sudden in onset and the exact hour was frequently known. At Camp Patrick Henry, in contrast, 70 percent of the patients noted a gradual onset. These, however, represented the milder cases discovered by careful case-finding studies and would not have been observed in the Apennines epidemic in which only patients with complaints sufficient to require hospitalization were seen. The early symptoms were nonspecific—chilliness, sweats, general malaise, weakness, fatigue, muscular aches, frontal headache, and anorexia. Pain in the chest when present was variable in intensity, ranging from a vague to a definitely pleuritic character.

Symptoms.—Although the onset was usually sudden, it was seldom severe enough to cause prostration, and the patient often continued duty for 12 to 72 hours. The nonspecific symptoms persisted and became more pronounced with the ensuing rise in temperature. Frank rigor was seldom experienced. Frontal headache was common and severe, as in many rickettsial diseases, and a majority of the patients complained of retro-orbital pain aggravated by coughing. Anorexia was the only common gastrointestinal symptom. A moderately dry cough frequently developed on the fifth or sixth day but was

not an outstanding feature. Approximately 20 percent of the patients who were carefully observed raised small amounts of blood-streaked sputum. Vague pain in the chest of the type described at the onset persisted, but true pleuritic pain was not common and was rarely severe, responding to aspirin and codeine therapy.

Physical findings.—Temperature on admission ranged between 101° and 105° F. The curve was irregular, extremely sensitive in a transient fashion to salicylates, and persisted from 4 to 15 days. It returned to normal by lysis with an occasional crisis. Slight relative bradycardia, normal respiratory rate, and absence of cyanosis and dyspnea were usual. A cutaneous rash was seen only in the first patient. Physical findings in the chest were normal or only minimally altered. Crepitant rales and slight diminution of breath sounds or dullness were occasionally noted, after the roentgenogram called attention to abnormalities. Coryza and pharyngitis were not encountered although vesicles on the pharyngeal mucuous membrane were noted in the epidemic in British paratroopers. Splenomegaly was rare save in the British paratroopers who also had generalized glandular enlargement. Herpes simplex was not observed. Nuchal rigidity of moderate intensity was seen occasionally, but in six patients, lumbar punctures yielded normal spinal fluid. Guinea pigs inoculated with one of these fluids obtained from a patient in the Apennines outbreak had a transmissible disease, but serological proof for its rickettsial origin, that is, cross-immunity, was not obtained.

Roentgenological findings.—The pneumonic infiltration as seen in roentgenograms was characteristic. Its incidence in all the outbreaks was not determined, but 80 percent of the proved cases in the Naples laboratory outbreak and 90 percent of those at Camp Patrick Henry showed such infiltration. The shadows were homogeneous, of a ground glass appearance and patchy in distribution, involving only a small portion of a lobe. Atelectasis with shift of an interlobar septum was frequently seen. In Italy, in most instances, lesions of a single lobe were observed, but occasionally, two lobes were affected. At Camp Patrick Henry, 60 percent of the patients had multilobar involvement. Lower lobe involvement predominated. There was no correlation between the extent of involvement demonstrated by roentgenogram and the severity of the disease. The roentgenogram of the chest on admission was frequently clear, with shadows appearing on the third or fourth, and occasionally as late as the sixth, day of the disease. Shadows consistent with small amounts of pleural fluid were seen in approximately 10 percent of the patients. The roentgenographic changes tended to be persistent and, frequently, were still present when the patient was discharged after an average stay of 22 days in the hospital. Resolution occurred by a gradual clearing of the involved area.

Course and convalescence.— With defervescence, the symptoms rapidly subsided leaving only weakness, which varied with the severity of the disease. The duration of asthenia ranged from a day to 3 weeks. Loss in weight

commensurate with a febrile illness associated with anorexia was usually observed. No deaths, no recurrences, and only one possible complication were seen in military personnel. The complication was a severe esophagitis in one patient in the Naples laboratory outbreak. The great majority of patients returned promptly to full duty.

Laboratory findings.—Increase in numbers of leukocytes, polymorphonuclear leukocytosis, and anemia were not observed. The urine was normal except for occasional mild albuminuria at the height of fever. The erythrocyte sedimentation rate was moderately rapid during the acute phase of illness and became normal promptly after recovery. Blood cultures were sterile; enteric agglutinations, *Proteus* OX-19, OX-2, and OX-K agglutination (save in the original Apennines patient), coccidioidin skin tests, and throat cultures were negative. Cold agglutinins, antibodies to influenza A and B, treatment with the sulfonamides or penicillin were noted.

Treatment.—Treatment was symptomatic, and no beneficial effects of treatment with the sulfonamides or penicillin were noted.

EPIDEMIOLOGY

The Henzerling strain isolated in Italy, the "Balkan grippe" strain from Greece, and the strains isolated in the laboratory outbreak at Fort Bragg and in Panama were similar in immunological specificity (complete reciprocal cross-immunity) to the rickettsia isolated by Dyer[6] (the American strain) although there were great variations in the sensitivity of the antigens. Cross-immunity between the Australian[7] and American strains had previously been demonstrated. It therefore seems reasonable to assume that the rickettsial disease seen in the Mediterranean area and in Panama characterized by pneumonitis was Q fever. The relationship of Q fever to the usual form of primary atypical pneumonia was investigated serologically, and it was found to be close in endemic areas such as Caserta, Italy, but not in nonendemic areas such as the Eastern United States.

Mode of transmission.—In the original cases from Australia, pneumonitis was not mentioned. The disease, there, is tickborne to cattle with a reservoir in bandicoots. The infection in man is aberrant, and the Australian workers postulated that the inhalation of dried tick feces present on the hides of cattle was the route of infection in human disease. Pneumonitis was first recognized in the laboratory epidemic at the National Institute of Health, U.S. Public Health Service,[8] and in retrospect, it appears that this was probably a dustborne rickettsial infection. No insect vectors were implicated in the Italian or Greek disease, but dusty habitations were noted. Retrospectively, in view of the isolation of rickettsiae from dust in California,[9] it

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6 See footnote 3 (2), p. 103.
7 See footnote 2 (2), p. 103.
8 See footnote 3 (3), p. 103.
9 See footnote 5, p. 105.

seems fair to assume that pneumonic Q fever may represent an infection in which the pulmonary infiltrate represents the primary lesion, as does the eschar in fièvre boutonneuse and rickettsialpox.

Military significance.—The military implications of this disease can be far-reaching. It occurs in sharp outbreaks and, although rarely fatal, can completely incapacitate an entire unit for combat. A satisfactory form of prophylaxis was not at hand during the war years. Since World War II, it has been shown that oxytetracycline (Terramycin) and chlortetracycline (Aureomycin) are effective in the treatment of Q fever.[10] The avoidance of dusty bivouacs in habitations where sheep, goats, or cattle have been kept may help, and disturbing of such dust by vigorous procedures should particularly be avoided.

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[10] (1) Stokes, M. G. P.: Q Fever in Britain. Brit. M. Bull. 9: 231-233, 1953. (2) See footnote 4, p. 103.

CHAPTER VI

Scrub Typhus

Chris J. D. Zarafonetis, M.D., and Myles P. Baker, M.D.

Scrub (or miteborne) typhus is an acute febrile disease caused by infection with *Rickettsia tsutsugamushi.* Clinically, it resembles other rickettsial diseases with an abrupt onset characterized by chilly sensations or rigors, followed by fever, headache, malaise, and later a rash. The differential diagnosis may be established early by finding the primary sore or eschar at the site of infection, often with associated satellite or generalized lymphadenopathy; at a later stage, some cases may be distinguished serologically. Scrub typhus is also called tsutsugamushi disease, tropical typhus, rural typhus, Japanese river fever, and Kedani fever.[1]

The earliest description of the malady in the Japanese literature was written by Hakuju Hashimoto in 1810, while the first English report was made by Palm in 1878. Mites were suspected as the probable vectors as early as 1879. The field mouse, *Microtus montebelli*, was implicated as an important natural reservoir of infection in 1918.

During the 20 years before World War II, careful research work, notably in Malaya and Sumatra, had indicated that tsutsugamushi disease was not limited to Northwestern Japan, Formosa, and the Pescadores Islands, where the Japanese had by 1931 definitely established its rickettsial etiology. The clinical picture, pathology, and epidemiology were shown to be fundamentally the same in Sumatran mite fever, in the scrub typhus of Malaya, the endemic typhus of New Guinea, the coastal fever of North Queensland, Australia, and in cases reported from Burma and Indochina. The common pattern could be traced in spite of wide variations in mortality and frequent failures to find the primary eschar. Prior to the experience of World War II, however, the only species of mite proved by animal experiments to be the vector of tsutsugamushi disease was the trombiculid mite identified by Japanese workers. Other mites had been highly suspected in Sumatra and Malaya, but conclusive proof had not been furnished. Similarly, the principal reservoir host of the trombiculid mite had not been incriminated elsewhere than in Japan and Malaya. Definitive work on the mite-rat complex, in New Guinea and Burma, remained to be done.

This identification of scrub typhus, as it was commonly called in the Armed Forces, with tsutsugamushi disease of the Japanese removes it from the list of strictly tropical diseases, for Japan can scarcely be considered

[1] Blake, F. G., Maxcy, K. F., Sadusk, J. F., Jr., Kohls, G. M., and Bell, E.J.: Studies on Tsutsugamushi Disease (Scrub Typhus, Mite-Borne Typhus) in New Guinea and Adjacent Islands; Epidemiology, Clinical Observations and Etiology in the Dobodura Area. Am. J. Hyg. 41: 243–373, May 1945.

within the tropics. It was, in fact, little known outside Japan as late as 1942. Its distribution is known to us now only as indicated by the accident of human infection with *R. tsutsugamushi.* With the advent of large-scale jungle warfare, scrub typhus became an important medical problem to troops in the Far East. Indeed, approximately 6,000 cases were to appear in U.S. Forces alone during the campaigns that followed the outbreak of war with Japan.

As military operations progressed in the Southwest Pacific and in Burma, U.S. Armed Forces passed into and through areas hitherto scarcely studied as to prevalent diseases and lived there under field conditions very unlike the customary sheltered life of the white planter of prewar years. One immediate result was a wider appreciation of the geographic area of distribution of this disease. Until then, such places as Bougainville and Goodenough Islands, the Schouten Islands, and Netherlands New Guinea, or Luzon and Mindoro Islands in the Philippines, had not been reported as sites of scrub typhus. Medical officers became acquainted at first hand with the clinical picture and pathology of the disease and had opportunity to compare it with other rickettsial infections, notably epidemic typhus. Opportunity was afforded for thorough study of its epidemiological and entomological aspects in the field and laboratory and for the institution of preventive measures.

CLINICAL EXPERIENCE

Southwest Pacific Area

In this region, Gunther had by 1940 collected 105 cases of a disease which he labeled "endemic typhus," chiefly from the Wau area in the mountains south of the Markham Valley in northeast New Guinea.[2] The clinical picture was described by him at length, the similarity to tsutsugamushi disease emphasized. Diagnostic agglutinations with *Proteus* OX–K were reported. The patients were white men who had been clearing jungle areas. Scattered cases were reported from New Britain Island and the coastline of northeast New Guinea west of Finschhafen. The disease was, then, well known when American and Australian Armed Forces moved into New Guinea in the spring of 1942.

THE FIRST PHASE: ORIENTATION (1942)

The first cases.—Typhus fever was first recognized among our troops in the Southwest Pacific as an isolated case, reported from northern Queensland in March 1942. Eight cases were reported from the Port Moresby area of Papua late in September 1942, and subsequently, a few cases appeared in the Milne Bay area at the eastern extremity of Papua.[3] During the summer

[2] Gunther, C. E. M.: A Survey of Endemic Typhus in New Guinea. Med. J. Australia 2: 564–573, 30 Nov. 1940.

[3] Essential Technical Medical Data, Southwest Pacific Area, for February 1944.

and early autumn of 1942, combat operations in Papua were primarily the assignment of Australian forces. At the close of the year, Lt. Col. S. W. Williams, of the 2/9th Australian General Hospital at Port Moresby, was able to report a preliminary study of 300 cases of scrub typhus.[4] Within 10 miles of Port Moresby, the disease was rare, considering the large number of troops concentrated there; all but a handful of these cases developed under combat conditions along the Moresby-Buna track, the so-called Kokoda Trail. This early Australian experience tallied closely with the prewar description of the clinical picture given by Gunther. Emphasis was laid on the following points:

Among the first hundred patients there was only one death; among the second hundred, exposed to the hardships of living conditions while following the Japanese retreat over the Owen Stanley Range, there were three deaths. In cases observed during December 1942, chiefly from the Buna-Gona combat area, the mortality was "nearly 10 percent." These soldiers, too, were spent by weeks of campaigning in the mountains and fighting around Buna.

Early diagnosis was not found a simple matter. Eschars were noted in only 60 percent of the cases. As experience was to show, they should be sought in covered parts of the body. Similarly, the rash was observed in about 60 percent only. Generalized lymph node enlargement was the most useful diagnostic sign in distinguishing the disease, in the early stages, from malaria. Even so, the diagnosis, in absence of eschar and rash, might well remain in doubt until the appearance of blood agglutinins for *Proteus* OX–K on about the 9th or 10th day of fever. It was noted that patients with scrub typhus fever may appear deceptively well during the first week, only to develop serious pulmonary, circulatory, and neurological symptoms in the second week of fever.

American troops were soon presenting examples of those diagnostic problems that proved to be scrub typhus. The majority of men who were to engage in combat in the Buna-Gona area were flown over "The Hump" of the Owen Stanleys, were set down at Dobodura airstrips, and went into battle late in November 1942. Patients with scrub typhus began to appear in December in Port Moresby hospitals, evacuated thereto by air. In January 1943, there was a sharp rise in the number of reported cases of scrub typhus in the Southwest Pacific Area (table 12). The case fatality rate for 1943 was 5.5 percent per 100 cases. In 1944, over 4,000 cases of scrub typhus were reported with a case fatality rate of 3.8 percent. During the first 8 months of 1945, the number of cases was less than those reported for the same period in 1943, with a case fatality rate of 5.4 percent. Owing to the exigencies of the military situation, soldiers convalescing from scrub typhus were evacuated to general hospitals on the Australian mainland, with the result that any compilation of case material was rendered impracticable. Medical officers in hos-

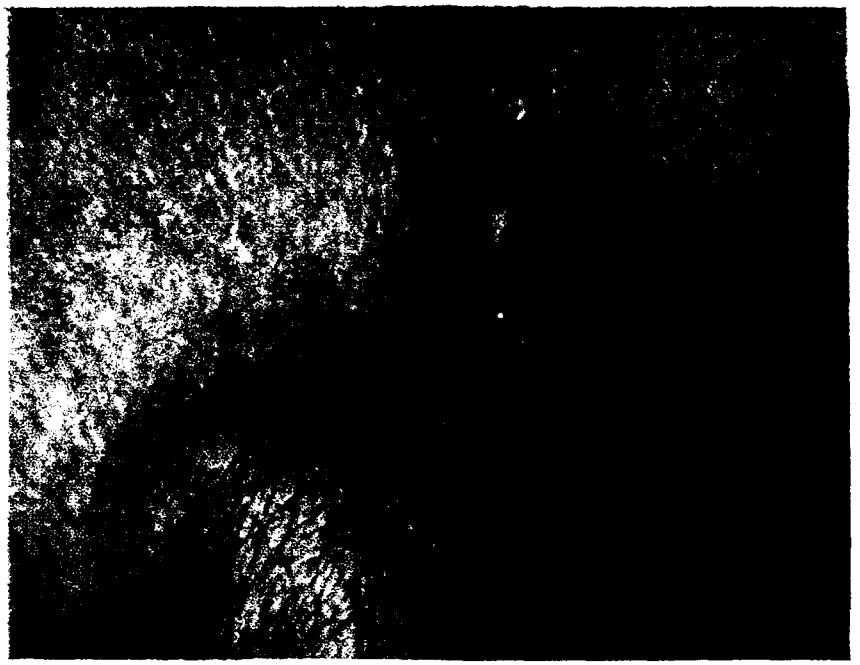
[4] Williams, S. W.: Scrub Typhus in Papua. Preliminary Report. A Description Founded on Observation of 300 Cases by the Medical Staff of an Australian General Hospital, 5 Jan. 1943. [Official record.]

TABLE 12.—*Number of cases and deaths due to scrub typhus in the Southwest Pacific Area, U.S. Army, January 1943 to August 1945*

[Preliminary data based on unit summary reports]

Period	Cases	Deaths
1943		
January	92	4
February	62	1
March	45	5
April	55	2
May	64	0
June	79	5
July	83	6
August	81	3
September	95	5
October	93	4
November	67	3
December	119	13
Total	935	51
1944		
January	75	9
February	104	16
March	184	8
April	75	12
May	130	4
June	212	15
July	647	9
August	1, 759	32
September	757	38
October	251	10
November	113	6
December	89	6
Total	4, 396	165
1945		
January	100	5
February	66	2
March	45	4
April	32	2
May	15	2
June	43	2
July	20	1
August	11	0
Total	332	18
Grand total	5, 663	234

pitals of the Advance Base, becoming familiar with clinical features of the textbook picture of the disease, cultivated a high index of suspicion of scrub typhus in the case classified as fever of undetermined origin with no evidence of malaria, no leukocytosis, no clinical response to Atabrine (quinacrine hydrochloride) or quinine, and with generalized lymph node enlargement. Eschars were more carefully sought for, and ulcers, without a scab, were found in the groins and axilla (fig. 8). By the time that agglutinins for



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FIGURE 8.—"Ulcer" eschar on right axilla in tsutsugamushi fever on 15th day of illness, 363d Station Hospital, Dobodura area, Papua.

Proteus OX–K appeared in the blood, the temperature curve had become diagnostically characteristic in cases without other diagnostic signs. One temperature chart (often making up the bulk of the record evacuated with the convalescent) could be superimposed on another, so alike were they.

In one series of cases,[5] the temperature was usually 99° to 102° F. on the first day of illness. There was a rise in temperature within 24 hours to 100° to 103° F., and during the days that followed, the 4-hourly chart showed a swinging temperature with daily remissions from 99° to 104° F. throughout the illness, subsiding by lysis on the 14th to 17th days. In the more severe cases, for the first 3 to 5 days a remittent type of fever was seen, followed by a sustained fever up to 105° F. until recovery or death. In some fatal cases a remittent fever ranging from 99° to 106° F. was recorded. A temperature which did not rise above 103° F. was seen in a few fatal cases.

The first necropsies.—Inexperience with the disease and lack of any specific treatment lent particular interest to the pathologist's findings in the first

[5] Williams, S. W., Sinclair, A. J. M., and Jackson, A. V.: Mite-Borne (Scrub) Typhus in Papua and the Mandated Territory of New Guinea: Report of 626 Cases. Med. J. Australia 2: 525-539, 18 Nov. 1944.

seven necropsies performed in December 1942 and January 1943 at Port Moresby by Capt. (later Maj.) Austin J. Corbett, MC.[6] He reported three groups of findings, as follows:

1. An acute diffuse myocarditis, with perivascular and interstitial infiltration with plasma cells, macrophages, and lymphocytes, as a constant and characteristic finding. Damage to the myocardial fibers varied in degree. Arteriolar walls showed thickening, degeneration, and intramural round-cell infiltration.

2. In the lungs, alveolar septa were infiltrated with mononuclear cells in a perivascular arrangement, and the vascular endothelium within the septa was swollen and fragmented.

3. In the brain, perivascular proliferation of glial cells and infiltration with lymphocytes were observed; the endothelium of smaller blood vessels was swollen, and several vessels showed intramural round-cell infiltration.

Cardiac findings and prognosis.—The finding of a diffuse myocardial lesion at autopsy, and the occasional finding of gallop rhythm and "soft" heart sounds on physical examination of the precariously balanced patient in the second and third weeks of fever, gave rise to much concern about the convalescent's prognosis. In the rear hospitals, in Australia, convalescents were examined carefully for evidence of residual cardiac damage and insufficiency and were found to have none. Pending the accumulation of enough data to support a general policy of sending all but the most hard-hit cases back to duty, the majority of convalescents were returned to duty following maximum hospitalization benefit.

THE SECOND PHASE: INVESTIGATIONS (1943)

A second phase in U.S. Army experience with scrub typhus began in the summer of 1943. The occurrence of cases from month to month, without seasonal incidence, was unremitting among combat and service troops, which were increasing in number as the bases were developed along the north coast of New Guinea to Finschhafen. The New Guinea hospitals had become more stabilized, facilitating the study of cases. This period saw clinical and epidemiological studies carried out by a group of investigators, headed by Dr. Francis G. Blake, working under the auspices of the United States of America Typhus Commission, and it saw also the development of preventive measures to protect troops from scrub typhus.

Clinical study.—It will be noted in table 12 that cases were diagnosed without letup during the spring and summer of 1943. Base B, which included Dobodura and Oro Bay, Papua, became a hive of activity with ever-increasing numbers of troops moving into camp areas in the base. Between 1 August and 1 December 1943, 248 patients with scrub typhus were admitted to Base B hospitals. The mortality in these cases was 2.4 percent. From a study of a group of 20 cases, most of them at the 363d Station Hospital, Dr. Blake and

[6] Corbett, A. J.: Scrub Typhus. Bull. U.S. Army M. Dept. No. 70, pp. 34-54, November 1943.

his collaborators constructed an exemplary word picture of the disease, as follows:[7]

The characteristic early symptoms and physical signs of mite typhus at onset and during the first 5 to 7 days of the disease are headache, apathy and generalized malaise, fever, relative bradycardia, anorexia, conjunctival congestion, lymphadenitis, often regional, and eschar. Although the diagnosis may be suspected from the general symptoms and physical signs together with a normal or low leukocyte count, only the presence of a typical eschar is sufficiently pathognomonic to establish the diagnosis at this stage of the disease. Consequently, the whole body surface should be scrutinized in detail with adequate light; unless this is done, the eschar may be easily overlooked if it is located in the less readily accessible areas.

Commonly, between the fifth and eighth days a characteristic macular or maculopapular rash appears on the trunk and may later spread to the extremities. It should be borne in mind, however, that although the development of a rash tends to confirm the suspected diagnosis, rashes sufficiently similar to that of mite typhus to cause confusion may at times occur in dengue and other infections.

The subsequent course of tsutsugamushi disease after the first week may be relatively mild, with no recognizable evidence of the more serious aspects of the disease, and with a total febrile period of 12 to 14 days; or moderately severe with signs of pneumonitis and encephalitis and recovery by lysis early in the third week; or severe to extremely severe with febrile course of approximately 3 weeks' duration. Symptoms and signs of more severe pneumonitis and encephalitis are constant. Evidence of peripheral circulatory collapse are common and signs of myocarditis may appear. Hepatitis and nephritis sometimes complicate the picture. Thromboses and cerebral or gastrointestinal hemorrhage may take place. Death is not infrequent in these severe cases, particularly in older individuals, but the majority recover by lysis during the latter half of the third week.

Laboratory studies have confirmed the already known fact that the Weil-Felix test becomes positive for *Proteus* OX-K about the 12th to 14th day of the disease in the majority of cases but that not all patients develop agglutinins for this organism in a diagnostic titer of 1 in 160 or higher. *Rickettsia orientalis* (tsutsugamushi) may readily be recovered from the blood of patients during the acute stage of the disease by the intraperitoneal inoculation of 0.2 to 0.3 ml. of blood into white mice. Both of these laboratory procedures, if positive, establish the diagnosis, but a negative Weil-Felix test for *Proteus* OX-K does not exclude miteborne typhus.

The total leukocyte count, usually within the normal range during the first week but sometimes showing a leukopenia, tends to increase during the second week. In cases progressing favorably, this leukocytosis is commonly due in large part to a progressive increase in the absolute number of lymphocytes.

Limited observations on the blood chemistry of the miteborne typhus of New Guinea have shown that hypochloremia, a moderate but not critical reduction in serum albumin, a rise in serum globulin, and a diminution in plasma fibrinogen tend to occur during the height of the disease.

The treatment of mite typhus consists primarily of complete bed rest, good nursing care, adequate diet, fluid and salt intake, and the judicious and selective use of symptomatic drug, supportive, and oxygen therapy only when specifically indicated. Penicillin is ineffective.

Blake and his coworkers particularly emphasized the localization above thigh level of the eschar, or primary ulceration, present in all 20 of their cases. This is in contradistinction to the bites of mites causing scrub itch, on the

[7] See footnote 1, p. 111.

ankles and shins. This observation tallied with that of the Australians at Port Moresby (65 percent on arms, axilla, neck, and trunk). They emphasized further (1) the absence of signs of right-sided heart failure, (2) the picture of a true rickettsial pneumonitis, with which physical signs and findings at autopsy are in keeping, and (3) the relation of cyanosis and pulmonary congestion to pneumonitis, rather than to myocardial insufficiency.

During the spring and summer of 1943, Australian patients were held at the general hospitals in Port Moresby, as American patients were not, making possible certain observations on 626 cases[8] that added to the clinical picture.

Significantly, as regards course, a few cases were recognized in ambulatory patients not sick enough to go off duty, but later showing agglutinins to *Proteus* OX-K of 1: 125 or higher (taken as a minimum diagnostic titer in this series). No relapse of fever attributable to the rickettsial infection was observed. Among symptoms, macules were noted on the soft palate, in association with the typical rash over the body.

In the severe cases, cardiovascular abnormalities such as faint systolic murmurs, tic-tac sounds, gallop rhythm, tachycardia, hypotension, and pulsus alternans were occasionally observed. Measurements of venous pressure and electrocardiographic study did not speak for myocardial insufficiency or clinically demonstrable myocarditis. Hearts examined microscopically in patients dying in the sixth week of complications not referable to circulatory apparatus showed no infiltration or fibrosis.

Cyanosis and increased respiratory rate accompanied the development of abnormal physical signs in the lungs, which did not include those of consolidation unless there was secondary infection, atelectasis, or infarction. Pulmonary infarction was a late complication to be reckoned with.

In the severely ill, mental symptoms uniformly appeared from about the 6th to the 10th day; apathy was more common than restless irritability and insomnia. Nerve deafness was present in 90 cases, and could be expected to be transient, lasting only a week. Paresis of the shoulder girdle muscles and sensory changes in arms and legs were observed during convalescence. Tremors of the hands appearing in the difficult second week were rare but striking, in one instance simulating the tremor of parkinsonism. Examinations of cerebrospinal fluid (60) revealed an increase in pressure (about 160 mm.) in less than half the individuals tapped; increase in lymphocyte count was infrequent (7 cases).

Mortality continued to vary much during the period of investigation; it rose from 1 to 2 percent in the first 200 cases to 25 percent in the next 150 cases, comprising soldiers exhausted by weeks of jungle combat, and handicapped by slow evacuation. For the next 276 cases, mortality was 7.2 percent. This varying mortality gives a fairer picture than the overall figure for 626 cases, 9.7 percent.

If, prior to evacuation, the soldier was seriously ill by the sixth day, or had already had 6 days of fever, it was thought wiser, if possible, to treat him "where he lies," rather than subject him to evacuation. Most patients were treated in convalescence in the expectancy that they would be fit to return to duty wihin 12 weeks from onset of their illness.

Lipman, Casey, Byron, and Evans reported a study of 200 patients observed at the 362d Station Hospital in Base B between February 1943 and February 1944.[9] The clinical picture in their cases conformed with Blake's. Their extensive experience permitted observation of complications that should

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[8] See footnote 5, p. 115.

[9] Lipman, B. L., Casey, A. V., Byron, R. A., and Evans, E. C.: Scrub Typhus; Results of a Study of the Cases of Two Hundred Patients Admitted To and Treated At a Station Hospital Between Feb. 9, 1943, and Feb. 4, 1944. War Med. 6: 304-315, November 1944.

be borne in mind; that is, pleural effusion, 5 percent; peripheral neuritis, ulnar, 5 percent; thrombophlebitis, 5 percent; and pulmonary and splenic infarction, each 2.5 percent. The mortality in their 200 cases was 10 percent. They emphasize the point made by the Australians at Port Moresby, that combat troops who will or must disregard early symptoms of scrub typhus are those with whom it goes hard. The older age group tolerated the onslaught of scrub typhus less well than did those younger. Six of the thirteen officers in this series died; four of the six were over 35 years of age. In therapy, these authors recommend the following: (1) A lumbar puncture for relief of meningismus and cerebral symptoms associated with an elevated spinal fluid pressure, (2) treatment of incipient and established peripheral vascular failure with oxygen and intravenous plasma, and (3) penicillin for secondary bronchopneumonia complicating the rickettsial pneumonitis.

Irons and Armbrust, at the 3d Medical Laboratory in Base B, extended their observations on the Weil-Felix reaction to a series of 74 cases of scrub typhus.[10]

Of this series, 86 percent developed blood agglutinins for *Proteus* OX–K. Controls with other febrile diseases gave negative reactions. In general, however, the incidence, maximum titer, and duration of the reaction were inversely proportional to the severity of the disease. Only 2 of the 7 fatal cases showed a positive Weil-Felix reaction during their clinical course; the maximum titer was 1:80. Patients with less than 18 days of fever were more likely to develop a titer of 1:160 or over than were those with longer febrile periods. The initial Weil-Felix reaction occurred at approximately the 17th day of the disease, after the peak in severity of clinical manifestations, or during obvious clinical improvement.

Accordingly, the authors concluded that the Weil-Felix reaction is of no value in prognosis. For diagnosis, no absolute level could be given, but a rise and fall in serial tests proved helpful in some cases. That a negative reaction does not exclude scrub typhus was indicated by isolation of the causative micro-organism in some cases with no OX–K titer.

Epidemiological study.—In addition to delineating the clinical features of scrub typhus, Blake and his coworkers clarified the epidemiological background of the disease, as follows:

> An analysis of the occurrence of cases among American forces in an advanced base area near Buna on the northeast coast of New Guinea indicated that, although the disease was contracted in widely scattered localities, some were more dangerous than others. It also indicated that the exposure to infection was associated with activities which brought men into intimate contact with field conditions, such as those which prevail in bivouacs or in establishing camps. During the period of this study in the Dobodura area, the environments in which human infections were known to have originated were kunai grass fields, in which natural conditions were undisturbed at the time of occupation. From the time distribution of onset of cases of the disease it was clear that maximum risk was experienced during the first week or two following arrival of a unit in a new area. This

[10] Irons, E. N., and Armbrust, C. A., Jr.: Relation of the Weil-Felix Reaction to the Clinical Course of Tsutsugamushi Disease. Bull. U.S. Army M. Dept. 5: 85–95, January 1946.

risk decreased progressively so that after the fourth or fifth week the incidence became sporadic or ceased entirely, and the site could be occupied with impunity thereafter.

Decline in the attack rate could not be explained as due to the accumulation of immune individuals. It therefore was probably due to decreased exposure to bites of some species of larval mites that served as vectors. Decrease in exposure was correlated with progressive changes produced by development and use of the campsite. Evidently, the conditions thus created were unfavorable to continued activity and survival of the vector species.

In attempting to identify this vector species, collections of larval mites were made not only in localities where cases had originated and extensive environmental changes taken place, but also in localities where the environment appeared to be similar but where the natural conditions remained undisturbed.

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* * * the observations made are consistent with the hypothesis that either *Trombicula fletcheri* or *Trombicula walchi*, or both, may serve as vectors in this area. Furthermore, by mouse inoculation, *R. orientalis* was recovered from two pools of mites (*T. fletcheri*) collected from two bandicoots. Brain tissue from these same animals, injected into white mice failed to produce a rickettsial infection. In view of this negative result and the fact that generation-to-generation transfer of *R. orientalis* occurs in mites, the evidence does not incriminate the bandicoot as a reservoir host.

This concept of bivouacs and the establishment of campsites as the background of scrub typhus was entirely in keeping with U.S. Army experience during 1943, elsewhere than at Dobodura. On 5 September 1943, the 503d Parachute Infantry Regiment jumped in the Markham Valley terrain which included much open grassy country with kunai grass prevailing. The regiment remained in jungle combat for about 12 days. By October, 37 cases of scrub typhus had appeared.[11] For the next 5 to 6 months, cases continued to occur as areas were developed around the Nadzab airstrips northwest of Lae in northeast New Guinea.

Outbreaks.—In November 1943, an epidemic of scrub typhus broke out on Goodenough Island, north of Papua, chiefly in a hospital area situated in kunai grass. For the first few nights after arrival in the area, personnel lived under conditions prevailing in the field. This was a serious outbreak. Seventy-five cases occurred on the island over the subsequent 4 months, most of them in December. The mortality, 25 percent, was uniquely high and cannot be adequately explained with the knowledge at hand. The patients were not in combat and were not exhausted when stricken. With each successive beachhead taken, cases of scrub typhus developed. The landing at Cape Gloucester in the Bismarck Archipelago was made in December 1943. At the 30th Evacuation Hospital, 104 cases were reported in February with 5 deaths; in March, there were 51 cases with 8 deaths. The mortality was 8.3 percent for these New Britain cases, more in keeping with the Dobodura series.[12] It is well to note, however, that in the first 3 months of 1944 the 363d Station Hospital at Dobodura had 60 cases of scrub typhus, of which 9 ended fatally, a mortality of 15 percent, in contrast to an average of 7.1 percent for the

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[11] See footnote 3, p. 112.

[12] Quarterly Report, Surgeon, 30th Evacuation Hospital (Semimobile), Southwest Pacific Area, 1 Jan.-31 Mar. 1944.

Dobodura region.[13] Eight of the deaths occurred in the first 35 cases admitted after transfer from the combat areas several hundred miles to the west. The patient sick with scrub typhus did not tolerate evacuation well.

Following the landing at Saidor in northeast New Guinea in January 1944, 61 cases developed in March, 59 of them among troops on patrols or bivouacked in a combat area. At Aitape, on the northwest coast, the same story held true: Landings on 22 April and 33 cases of scrub typhus in May, 52 in June, and continued incidence in July and August. Headquarters, 32d Infantry Division, proffered the comments that the cases developed in fairly well identified areas, or in troops on patrol, that withdrawal from the perimeter to cleared areas caused a dwindling of cases, and that uncleared kunai grass and low sites where kunai grass and underbrush are mingled are dangerous. At Hollandia in Netherlands New Guinea, there were scattered cases; 43 of the 140 reported for the Sixth U.S. Army in June originated there. It is worthy of note that the new staging area for the 32d Division at Hollandia was burned over before troops were allowed to move into it in September. During the ensuing month, there were no cases reported from this area. An engineer aviation battalion that moved into Hollandia late in April reported 24 cases with 7 deaths in May and June, "due to sleeping in kunai grass, since no tents or cots were available the first month." The small Wakde Task Force that captured this island with its important airstrip in May reported a few cases in the third and fourth weeks of June.[14]

It is to be noted that task force units were becoming familiar with the type of terrain to be avoided and the dangers of sleeping on or near the ground in uncleared areas likely to harbor infected mites. Meanwhile, active measures for personnel protection of the soldier were in preparation.

THE THIRD PHASE: PEAK OF INCIDENCE AND CONTROL MEASURES (1944)

The subsequent epidemics at Owi and Biak (in the Schouten Islands) and at Sansapor (in Netherlands New Guinea) mark a third period in Army experience with scrub typhus, in which (1) the disease first assumed proportions serious from a military point of view, (2) new ecological types of foci appeared, and (3) procedures, long-planned, were directed at energetic control of the epidemics.

Outbreaks.—Cases first developed on Owi, a small island off the southern shore of Biak, about 10 to 14 days after arrival of units of the Army Air Forces early in June. During July and early August, as much as one-fourth to one-third of the effective personnel of two air force squadrons on Owi were hospitalized for scrub typhus. On nearby Biak, there were 107

[13] Kohls, G. M., Armbrust, C. A., Irons, E. N., and Philip, C. B.: Studies of Tsutsugamushi Disease (Scrub Typhus, Mite-Borne Typhus) in New Guinea and Adjacent Islands: Further Observations on Epidemiology and Etiology. Am. J. Hyg. 41: 374–396, May 1945.

[14] (1) Quarterly Report, Surgeon, Sixth U.S. Army, Southwest Pacific Area, 1 Apr.-30 June 1944. (2) Quarterly Report, 32d Infantry Division, plus attached units, Southwest Pacific Area, 1 July-30 Sept. 1944. (3) Quarterly Report, 1913th Engineer Aviation Battalion, Southwest Pacific Area, 1 Jan.-31 Mar. 1944.

cases in the 186th Infantry within 41 days of D-day, 32 of them from one company engaged in patrol in the island hills.[15] Certain units were unable to function effectively until replacements were secured. Owi and Biak are coralline, with bare ridges and porous outcrops, very little swampy land, no kunai flats, and few open grassy areas. Even where there is little topsoil, as on Owi, dense underbrush, ferns, and many immense rotting logs provide cover and moisture for mites. With New Guinea experience as precedent, scrub typhus was not expected in this type of terrain. The first cases were relatively mild, eschars were infrequent, and these fevers of undetermined origin were not directly recognized as scrub typhus. They were thought on Owi to be dengue fever until typical cases of scrub typhus appeared, and *Culex* mosquitoes were found to be scarce. The risk on Owi lay in the slowness in clearing of campsites. A contributing factor was the necessity for using all available bulldozers for the construction of airstrips. Men leaving clothes on rotting logs, when swimming in the ocean, may also have contributed. On Biak, severe fighting in uncleared areas, seeking cover in thick underbrush, and patrolling, all contributed to exposure to the infected mites.

Members of the U.S.A. Typhus Commission arrived at Owi soon after scrub typhus was recognized, and encouraged the speedy clearing of campsites and sanding of tent floors, together with impregnation of clothing. Emulsions of dimethyl phthalate were made available and all personnel were equipped with treated clothing within 2 weeks of arrival of the repellent.[16] The fall in incidence in the various units expressed the sum of the effect of control measures. On Biak, similarly, the 41st Infantry Division was in impregnated clothing by the second week in August and camp areas were cleared. The scrub typhus rate fell appreciably in the latter part of August.[17] The absorbingly interesting story of the development and institution of preventive measures against scrub typhus are recounted in another volume in the history of the Medical Department in World War II.[18]

The Owi-Biak outbreak included at least 1,080 cases, which passed through the 92d Evacuation Hospital. The mortality, 0.7 percent, was low, and many cases were milder than had been the experience in Papua.[19] No ill effects were noted from the air evacuation to Nadzab or Finschhafen of convalescents 5 days or more after defervescence.

The Sansapor task force landed at the western extremity of New Guinea

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[15] Essential Technical Medical Data, U.S. Army, Services of Supply, Southwest Pacific Area, for September 1944.

[16] Letter, Lt. Col. Cornelius B. Philip, SnC, to Surgeon, U.S. Army Forces in the Far East, 5 Aug. 1944, subject: Scrub Typhus on Owi and Biak Islands.

[17] Monthly Sanitary Report, 41st Infantry Division, Office of Surgeon, Southwest Pacific Area, October 1944.

[18] Philip, Cornelius B.: Scrub Typhus and Scrub Itch. *In* Medical Department, United States Army. Preventive Medicine in World War II. Volume VII. Communicable Diseases: Arthropodborne Diseases Other Than Malaria. [In preparation.]

[19] *Quarterly Report*, Surgeon, 92d Evacuation Hospital (Semimobile), Southwest Pacific Area, 1 July-30 Sept. 1944.

on 30 July 1944.[20] On 6 August, the first case of scrub typhus developed, an unusually short incubation period. The outbreak was explosive (135 cases by D+13) and a cause of serious depletion in strength. In one battalion, 17 percent (125 cases) were stricken. Impregnated clothing appeared to be definitely protective, when used. In all, about 931 cases (data are incomplete) were reported in the course of 53 days at Sansapor, with a mortality of 3.4 percent. Attempt was made to avoid a long 1,200-mile air evacuation until patients were afebrile. This led to much congestion at the one functioning evacuation hospital but was doubtless the better part of wisdom in view of the earlier experience in the Cape Gloucester and Aitape operations. At Sansapor, it was noted that areas of infection were found particularly in abandoned plantations or native gardens filled with a rank growth of grass. These areas, as at Owi-Biak, represented a different type of focus from those seen theretofore, and apparently in this instance a highly infected type, to judge from the high incidence of eschars and the recovery of *R. tsutsugamushi* from white mice injected with material from each of three lots of rat mites.

Convalescence and disposition.—The base hospitals to which the New Guinea cases were evacuated continued, over the course of the 20 months from January 1943 to August 1944, to determine the disposition of convalescent cases. Many ambulatory convalescents complained on admission of rapid heart rate and shortwindedness on slight exertion. Some litter cases were slow to mobilize themselves. At the 105th General Hospital in Australia, Levine carried out observations on 130 convalescents and found no evidence, by physical examination, electrocardiogram, roentgen examination, or by measurements of vital capacity or venous pressure, of persistent myocardial damage.[21]

Exercise tolerance tests gave mediocre results, which could be contributed to, commonly, by a prevalent anxiety state. Patients whose heart rates were rapid prior to a road march returned from a 5-mile march with normal heart rates. Such a functional test appeared more reliable than a "Schneider index" determination. Of this series of 130 patients, 117 were returned to full duty.

A critical evaluation by Howell of the 233d Station Hospital, at Nadzab, of electrocardiograms in 190 convalescents from scrub typhus (92 percent within 1 to 4 weeks after subsidence of fever) and 10 acute cases revealed no significantly abnormal electrocardiographic patterns.[22] There were minor deviations from normal, to be sure, and these were all too often exaggerated in importance by the unwary observer. But they were no more frequent than

[20] (1) See footnote 13, p. 121. (2) Quarterly Report, Surgeon, Headquarters, Sixth U.S. Army, Southwest Pacific Area, 1 July-30 Sept. 1944.

[21] Levine, H. D.: Cardiac Complications of Tsutsugamushi Fever (Scrub Typhus); An Investigation of Their Persistency. War Med. 7: 76–81, February 1945.

[22] Howell, W. L.: Absence of Electrocardiographic Changes in Tsutsugamushi Fever (Scrub Typhus). Report of 200 Consecutive Cases. Arch. Int. Med. 76: 217–218, October 1945.

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have been found in a series of tracings from approximately 500 healthy young adults.

In the summer of 1944, at the instigation of Col. Bruce P. Webster, MC, then Surgeon, Base E, a reconditioning program for scrub typhus convalescents was set up at the 90th Station Hospital. Three hundred and twelve unselected and successive patients were classified on admission with regard to their capacity for exercise.[23] Only 8 percent were considered to be, properly, bed cases. These patients had been evacuated chiefly from Owi-Biak, Sansapor, and Aitape. They had averaged 4 weeks prior hospitalization. In rare cases, there was residual hypesthesia and deafness. Tachycardia, tremors of the hands, and giddiness were frequent. At the completion of a purposeful, graded reconditioning program, 303, or 97 percent, were returned to full duty, after an average of 1 month in this hospital. These patients were symptom free on discharge, the majority with weight regained. Nine patients were evacuated to the rear because of associated disabilities, not referable directly to scrub typhus.

This policy of returning the scrub typhus convalescent to duty was thus supported as experience with the disease increased in 1944. Few such soldiers were subsequently evacuated for inability "to stand the gaff" of field duty. Technical Memorandum No. 10, Headquarters, United States Army Forces in the Far East, dated 29 August 1944, declared it official policy (1) that in patients who have safely reached convalescence from scrub typhus, complete recovery is to be expected, (2) that permanent physical defects resulting from the disease are exceptional, (3) that physical reconditioning, with unequivocal reassurance that there is no residual heart damage, will expedite recovery of stamina, and (4) that patients who require a month or more of full physical reconditioning should be transferred for that purpose to the newly established training center at Oro Bay.

The concept of the part that the myocardial lesion plays in scrub typhus had thus changed materially from that which prevailed early in 1943 when the first cases were observed, precariously ill, and at post mortem. Berry, Johnson, and Warshauer,[24] reporting experience with 85 cases and 110 convalescents in two New Guinea station hospitals between 20 December 1943 and 20 June 1944, drew the following conclusions:

1. Clinically, there is no severe irreversible myocardial damage.

2. Peripheral vascular collapse in the severely ill patient poses the therapeutic problem, not myocardial failure; the clinical picture is analogous to that of shock and should be treated accordingly.

3. Circulatory symptoms in convalescence are no more pronounced than after any severe infection.

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[23] Romeo, B. J.: Convalescence From Scrub Typhus. Bull. U.S. Army M. Dept. 6: 167–173, August 1946.

[24] Berry, M. G., Johnson, A. S., Jr., and Warshauer, S. E.: Tsutsugamushi Fever; Clinical Observation in One Hundred and Ninety-five Cases. War Med. 7: 71–75, February 1945.

4. The patient should not be given the impression that he has any heart disease.

The soundness of this policy was borne out by the report [25] from one general hospital in the Zone of Interior that examination of such patients as were returned from overseas with the diagnosis of myocarditis following scrub typhus fever definitely indicated their disability to be that of neurocirculatory asthenia.

Settle, Pinkerton, and Corbett [26] reviewed the pathological changes from 55 fatal cases of scrub typhus occurring in American troops in Papua, Netherlands New Guinea, and adjacent islands. They reassert that generalized acute vasculitis was a constant finding. But they note that although myocarditis was present in all cases, it was severe in only about half the patients, more commonly in those dying relatively early, between the 9th and 12th days of illness. They suggest that in these severe cases myocardial failure may contribute to fatality; yet they elect to emphasize the generalized vascular lesions and the concept that patients with rickettsial vasculitis may die of peripheral circulatory collapse. They draw attention to a similar conclusion of Woodward and Bland [27] from their cases of epidemic louseborne typhus in the Mediterranean Theater of Operations, U.S. Army.

IN THE PHILIPPINES (1945)

In the Philippine Islands, scrub typhus appeared sporadically during U.S. Army operations [28] but never to the degree of military importance it had assumed at Owi and Biak, and might have done at Sansapor had enemy resistance been more taxing. Scrub typhus had not been identified in the Philippines prior to World War II. Toward the close of the Leyte campaign, late in 1944, 3 cases were reported from the northern end of the island. Fifty-one cases were reported from Samar, where units of the Army did extensive patrol duty after the invasion of nearby Leyte. On Mindoro, experience with scrub typhus followed the typical course: Invasion in December 1944, the first case admitted to hospital 12 days after the initial landing, and the bulk of the 100 cases reported in January and early February. Sporadic cases continued for the next 3 months.

On Luzon, rare cases were identified from the mountainous country east of Manila during the fighting in February 1945. Diagnosis was based on the finding of classical eschars and a positive Weil-Felix reaction with the OX–K strain of *Proteus*. A cluster of three cases appeared early in May in one in-

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[25] Benjamin, J. E., Porter, R. R., and Dreisbach, R. H.: Sudden Death in Patient Supposed To Have Myocarditis Following Scrub Typhus. Bull. U.S. Army M. Dept. 4: 235–238, August 1945.

[26] Settle, E. B., Pinkerton, H., and Corbett, A. J.: A Pathologic Study of Tsutsugamushi Disease (Scrub Typhus) With Notes on Clinicopathologic Correlation. J. Lab. & Clin. Med. 30: 639–661, August 1945.

[27] Woodward, T. E., and Bland, E. F.: Clinical Observations in Typhus Fever, With Special Reference to the Cardiovascular System. J.A.M.A. 126: 287–293, 30 Sept. 1944.

[28] Essential Technical Medical Data, U.S. Army Forces, Pacific (for Western Pacific Area), May and June 1945.

fantry regiment engaged in battle in the mountains west of Baguio. A rising titer of OX–K agglutination was present in all three cases. All had a typical rash and clinical course, and one had an eschar. Beginning on 9 May 1945, cases of scrub typhus were recognized in a regiment engaged in a beachhead landing in the Bicol Peninsula in the southern end of Luzon. Six cases developed in the course of a week and four more in the following fortnight. Eschars were present in only 2 of the 10 cases, but clinical course, rash, and rising OX–K titers were diagnostic. During the combat of Negros in late April and May 1945, six cases appeared in two infantry units, all with eschars.

These reported data on approximately 180 cases are inevitably incomplete, for they do not include patients evacuated from Luzon for other medical reasons who developed scrub typhus en route to or after arrival at New Guinea base hospitals. Statistical reports on Southwest Pacific Area scrub typhus for 1945 include 258 cases up to 1 June (table 12) with a mortality of 5.8 percent. There was nothing unusual in the clinical picture of the cases in the Philippine Islands. Plasma and blood transfusions were used more frequently than in New Guinea days, to forestall or alleviate peripheral circulatory collapse. The number of cases so treated, however, did not permit any comparative study. In the focal areas of infection studied, as on Mindoro and Negros, cogon grass was prevalent. This was probably not so near Baguio. Bearing in mind the Owi-Biak experience, the U.S.A. Typhus Commission warned that any environment harboring rats infested with Trombiculae that will accept man as a casual host can be a potential source of human infection.

The Philippine experience with scrub typhus made it clear that when man exposes himself to field conditions wherein he may become an accidental host, scrub typhus will appear sporadically, and unpredictably, in hitherto unreported districts.

South Pacific Area

Before the war, scrub typhus had not been recognized in the Solomon Islands. The first case was identified on Bougainville in December 1943. Nine more cases developed in January 1944. All had been exposed in a bivouac area on the bank of the Laruma River. Sporadic cases, 11 in number, each after exposure in the same area, developed in the course of the next 6 months. In all but two of these cases, agglutinins for *Proteus* OX–K developed in a titer of 1:160 or higher.

An interesting outbreak of mild scrub typhus developed on Bougainville in a Fijian force of 750 who were bivouacked in a meadow of coarse grass between riverbank and jungle at the former site of a native village.[29] From 14 to 22 days later, 49 patients were in hospital with a fever that averaged 11 days' duration. An eschar typical of scrub typhus was found in all cases, and was above the legs in 32 (65 percent) of them. Generalized lymph node

[29] Anderson, W. L., and Wing, W. M.: Tsutsugamushi Disease (Scrub Typhus); A Clinical Study of 49 Cases. War Med. 8: 163-166, September 1945.

enlargement was constant; the eruption was present in 45 percent (22 patients). Bradycardia was the rule. Tachypnea was not observed. In these Fijians, in whom malaria could be excluded, the splenic enlargement was made out in the course of the second week in approximately 40 percent. *Proteus* OX–K agglutinins were present in 24 cases, or about 50 percent; only 5 had titers of 1:1,200 or over; 19 ranged from 1:50 to 1:200. Two weeks later, another patrol of the same strength wearing clothing impregnated with dimethyl phthalate bivouacked in the same area with no resultant cases of scrub typhus. Two months later, an unprotected patrol went into the same area. After they came out, 23 cases of scrub typhus appeared. The available evidence suggests that this was a localized focus of mild scrub typhus.

India-Burma Theater

Before the outbreak of hostilities in 1941, there had been considerable interest in Indian Army Medical Services in cases diagnosed as "fevers of the typhus group." It had become clear that there were two types in the Simla hill country: (1) The murine or flea typhus case, developing agglutinins for *Proteus* OX–19, occurred under urban conditions, such as the bazaar sections of the cantonments, and (2) scrub or mite typhus, with agglutinins for *Proteus* OX–Kingsbury strain, occurred sporadically or in explosive focal outbreaks in units living under field conditions, particularly in scrub jungle. Attempts to establish the presence of rickettsial infection in a larval mite had not been made, nor had it been possible to isolate a strain of OX–K typhus in a wild rat. The rodent reservoirs of mite typhus in India were not established. The disease had been known to exist in Burma since 1932.

The late months of 1943 marked a period of orientation in this disease for U.S. Army medical officers. During November, a group of 22 febrile patients were admitted to the 20th General Hospital at Ledo, Assam.[30] The fever was intense, associated with generalized lymphadenopathy, mild conjunctivitis, and on occasion a nonpetechial rash, appearing on the fifth to eighth day. Small ulcers or crusted papules were found and thought to mark the bite of the infecting insect. The fever lasted 8 to 20 days. The first Weil-Felix reactions were negative, save for a few agglutinations of OX–K in low titer. However, these patients, mostly Chinese troops in active training for jungle warfare, were considered likely cases of scrub (mite) typhus. In Shingbwiyang, Burma, on the Stilwell Road, 50 cases, entirely similar, had appeared in November. By 1 February 1944, 352 cases had been reported, 35 of them Americans, the remainder Chinese, all from units living under field conditions along the Stilwell Road. Two centers of infection where troops had been in training were incriminated, one of them the center of the jungle training area of the 22d Chinese Division, the other a campsite much fre-

[30] Letter, Maj. D. S. Pepper, MC, Assistant Chief, Medical Service, 20th General Hospital, to Surgeon, Base Section 3, China-Burma-India Theater, 9 Dec. 1943, subject: Report on Investigation of "C.B.I. Fever."

quented by Chinese troops. All American soldiers with scrub typhus had been living in the jungle. By December, the clinical picture had taken on a definite and characteristic pattern, in every way conforming to the picture of scrub typhus already familiar in the Southwest Pacific Area and to the descriptions of tsutsugamushi fever in Japan. Eschar, rash, fever curve, circulatory symptoms and signs, pneumonitis, and encephalitic manifestations were observed. Agglutinations in high titer for *Proteus* OX–K were found.

It was noted that the focal areas from which most of these Chinese cases came were not occupied by an appreciable number of troops until October 1943. During each of the last 2 weeks of November, there were 40 cases, and this rate rose to 60 per week through December. Incidence dropped off sharply in early January, following rather closely the movement of troops out of the area.

Earlier, in the autumn of 1943, a British unit in the India-Burma theater had 121 cases in an outbreak that began 9 days after moving into an area for training exercises.[31] The epidemic subsided directly after the area was left, with cases continuing in the unit for about 2 weeks. The description of their cases was in all respects similar to the Chinese and American groups.

Captured Japanese reports revealed that the enemy in Burma was encountering the same disease, which they called eruptive fever. They recognized similarity to tsutsugamushi fever but did not find the eschar frequently enough to warrant making this diagnosis in Burma. Their mortality rate is not given save in the comment—"very low." This incidence among the Japanese is all the more interesting in the light of our repeatedly negative reports about scrub typhus in enemy troops in New Guinea.

The subsequent story of scrub typhus among American troops in Burma is described in a comprehensive report by Sayen, Pond, Forrester, and Wood from the 20th General Hospital.[32] Up to July 1945, there were 726 cases reported from the India-Burma theater in U.S. Army personnel with 52 deaths, a mortality of 7.2 percent. Among U.S. Army troops, 535 cases were carefully studied at the 20th General Hospital; 472 of these Americans were acutely ill on admission. There were 27 deaths, giving a mortality of 5.7 percent.

Sayen and his coworkers point out that a more intelligent understanding of the severity of scrub typhus is gained from grouping their cases according to the circumstances surrounding the successive outbreaks. Among 113 American soldiers from Services of Supply units installed along the Ledo Road who developed the disease sporadically, the mortality was approximately 4 percent. Among 105 patients who were evacuated by air from active jungle combat in the mountains north of Myitkyina, Burma, from March to May 1944, the mortality was 16 percent. This group, exhausted by the stress of

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[31] Blumgart, Herman L., and Pike, George M.: History of Internal Medicine in India-Burma Theater. Chapter on Scrub Typhus, inclosure 5 thereto. [Official record.]

[32] Sayen, J. J., Pond, H. S., Forrester, J. S., and Wood, F. C.: Scrub Typhus in Assam and Burma; A Clinical Study of 616 Cases. Medicine 25: 155–214, May 1946.

fighting, and stricken with scrub typhus, was in an area from which evacuation was difficult. The mortality of only approximately 1.5 percent among 177 cases evacuated in the autumn of 1944 from troops undergoing jungle training north of Myitkyina must be related to speedy hospitalization in the forward area, and early evacuation to a general hospital. This group was in far better physical condition than the combat troops of the second group. In a fourth group of 77 cases, evacuated from combat south of Bhamo, Burma, in January and February 1945, the fatality rate rose again to 7 percent. Evacuation for this group was as difficult as for the Myitkyina combat group, marching after onset of fever again being unavoidable. The patient's pretyphus state of health and quality of early care were vital in prognosis.

The typical march of symptoms developed in all of these cases. Effort on the part of Sayen and his coworkers to classify the cases according to severity warrants quotation, as follows:

In the average case of scrub typhus, during the first week there were no signs by which the probable outcome could be determined. Occasionally a high fever at this time indicated a severe course. During the second and third weeks, however, certain phenomena appeared which justified placing the patient in "severe" or "grave" groups with respective mortalities of approximately 25 and 50 percent. However, until the disease was definitely on the decline one could not be sure that these features would not appear. Consequently, the diagnosis of "mild" or "moderate" scrub typhus, which carried practically no mortality, was not justified until defervescence was established. * * *

A case of scrub typhus was assigned to the "severe" group on the basis of any one of the following:

(1) An alarming increase of the general evidences of illness in the second week.

(2) More than the usual amount of fever: Over a week of peaks to 104°, or 105° for more than 2 days.

(3) Frank clinical signs of dysfunction of an important organ:

(a) Signs of "typhus pneumonitis": Respirations 36 per minute for 2 days; cyanosis of the skin.

(b) Signs of meningoencephalitis: Severe delirium; meningismus.

(c) Signs of nephritis: Azotemia over 50 mgm. percent, isosthenuria, heavy albuminuria and cylindruria.

(d) Marked enlargement of the heart or sharp T-wave inversion in the electrocardiogram.

(e) Pitting edema with or without ascites.

(f) Multiple hemorrhagic phenomena.

The appearance of any of these phenomena indicated that statistically the patient's chances of survival had been reduced from 19 in 20 to about 3 in 4.

A severe case of scrub typhus was considered in the "grave" group on the basis of one of the following findings:

(1) A steady increase of illness during the third week.

(2) Very high fever: 105° for 5 days or 106° for 2 days.

(3) Signs of severe dysfunction of more than one vital organ, or evidence of severe inflammation of the central nervous system and the lungs. Of these, the most common were the following:

(a) Extensive pneumonitis: Persistent cyanosis out of oxygen [tent]; respiratory rate 50 per minute for 2 days, or over 36 per minute for a week.

(b) Encephalitis: Malignant restlessness, Cheyne-Stokes respiration, a convulsion, coma.

(c) Severe nephritis: Anuria.

(d) Tachycardia exceeding 130 per minute.

The appearance of these phenomena indicated that, statistically, the patients' chances for survival were 25 to 50 percent. We have never seen a patient recover whose cyanosis was unrelieved by oxygen or who had persistent hyperpnoea, pulmonary edema, or coma lasting 24 hours.

In their discussion of the classical signs, laboratory findings, and treatment of scrub typhus, Sayen and his coworkers bring out the following interesting points that tally with or supplement findings recorded in the Southwest Pacific Area.

1. The finding of an ulcer or papule that later became a typical mite ulcer 1 to 14 days prior to onset of symptoms was not uncommon. The presence (60 percent of 200 cases) or character of the eschar or ulcer had no relation to the severity of the disease, or to the OX–K titer. In only 27 percent was the primary lesion on the thighs or below.

2. Increasing generalized enlargement with, usually, tenderness of the lymph nodes was an early development in all but 6 of the 200 patients, and was, in fact, the most constant of the main diagnostic clinical signs.

3. The eruption (71 percent of cases) involved the trunk always, the face in 15 percent. Generally of 4 to 9 days' duration, it might outlast the fever. A few rashes were florid or purpuric. There was no relation of the rash to the severity of the disease.

4. Ophthalmoscopic examination revealed engorgement of retinal veins in 67 percent of cases in the first and second weeks, progressing to bilateral edema of the retina and optic nerve head in 36 percent, with retinal hemorrhage and exudate in a few instances. Retinopathy of this sort was absent in other febrile disease, and was actually helpful in the early diagnosis of atypical cases, later confirmed by the OX–K agglutination reaction.[33]

5. Bronchial rales, changing in location, appeared in "mild" and "moderate" cases, did not of themselves indicate a rickettsial pneumonitis.

6. Brief periods of gallop rhythm were not evidence of a prognostically important degree of interstitial myocarditis.

7. Agglutination titers for *Proteus* OX–K of 1:100 were not seen except in scrub typhus. About half of a series of 200 cases failed to have this "diagnostic" titer. It was helpful diagnostically in isolated atypical cases. In epidemics, a "clinical" diagnosis was generally made before agglutination became positive (about the 14th day, on an average).

8. Cerebral malaria was the disease of chief importance to exclude in differential diagnosis of the case without conclusive signs of scrub typhus.

9. Roentgen examination of the chest in scrub typhus cases often failed to indicate the extent and severity of the rickettsial pneumonitis. Intermittent dyspnea at rest, then persistent tachypnea, and cyanosis relieved initially by oxygen comprised a march of signs more valuable than physical findings in

[33] For a further discussion of the ocular manifestations of scrub typhus (new and original work) see Medical Department, United States Army. Surgery in World War II. Ophthalmology and Otolaryngology. Washington: U.S. Government Printing Office, 1957, pp. 141–144.—J. B. C., Jr.

the chest or roentgen examination in establishing the presence of pneumonitis.

10. Cardiac enlargement, sharp T-wave inversion with or without RS-T elevation (11 percent of 61 cases suspected of cardiac complication), and persistent gallop rhythm were not found to be necessarily evidence of ill omen. Dangerous rickettsial myocarditis could not be diagnosed, prior to final collapse, save by inference of precedent. No patient with T-wave inversion died; three cases who had tracings before death showed no electrocardiographic abnormality.

11. Spinal fluids in 27 patients with signs of meningeal irritation were under increased pressure (average 230 mm. of water). Ten had increase in cells, generally lymphocytes; three had a polynuclear pleocytosis with negative cultures. Spinal fluid protein levels were elevated (68 to 156 mg. percent, in four cases).

12. Convulsions occurred in 12 patients, of whom 3 were not considered dangerously ill until the convulsive seizure.

13. Spontaneous diuresis late in the febrile course, or at the onset of convalescence, was observed in 38 percent of 200 cases; the largest diureses were seen in the sicker patients with edema (10 percent of face, hands, shins, and feet), and with ascites. It constituted a reassuring prognostic sign.

14. Hypochloremia was little modified by parenteral saline therapy. Return to normal blood chloride levels occurred in convalescence, regardless of therapy.

15. In convalescence, thrombophlebitis and pulmonary embolism were occasional complications. Pleurisy developed in 10 percent of 200 cases; effusions, if present, were small, sterile; fever lasted only 4 days, and evidence of pleurisy was generally gone in a week.

16. In treatment.—(1) The mildest appearing case in the first week should be prepared by absolute bed rest for an unpredictably severe ordeal in the second week. (2) An adequate number of experienced nurses is of vital importance to see that small frequent feedings are taken, fluids pushed (minimum of 3 liters daily), and severely ill patients protected. (3) Salt administration can be overdone; it may aggravate edema. (4) Oxygen should be given by mask preferably; when given by nasal catheter, it did not, in the average case, relieve cyanosis. (5) Rectal paraldehyde, 30 cc. in oil, was the best sedative for "malignant restlessness," and might make it possible for the cyanotic patient to tolerate oxygen by mask, and prevent exhausting exertion. (6) Digitalis was not used. (7) Penicillin was of no avail save in the presence of a complicating bronchopneumonia. (8) The concept of peripheral circulatory collapse was not raised; intravenous plasma was not used with this in mind. (9) Intravenous fluids were given when indicated, carefully, and without untoward incident.

As experience with scrub typhus increased, confidence grew in the convalescent's ability to cope with the demands of duty. Patients with mild and

moderate cases (less than 3 weeks of fever) were informed soon after defervescence that they were returning to their units and were gradually reconditioned for discharge about 3 to 4 months from the onset of illness. Patients who had been gravely ill were evacuated to the Zone of Interior. The severe cases were appraised individually. Of the last 300 cases, 82 percent were returned to full duty. No evidence of residual myocardial damage was detected during reconditioning.

PATHOLOGY

Although a number of reports [34] dealt with the pathology of scrub typhus, the most comprehensive study was performed at the Army Institute of Pathology (now the Armed Forces Institute of Pathology), Washington, D.C., by Maj. Arthur C. Allen, MC, and Dr. Sophie Spitz.[35] These workers undertook to study the lesions not only of scrub typhus, but also of louseborne typhus, Rocky Mountain spotted fever, and Q fever in order to determine whether the various rickettsial diseases could be differentiated histologically. After careful study of the histological preparations and protocols of 78 cases of scrub typhus, 24 cases of epidemic typhus, 12 cases of Rocky Mountain spotted fever, and lung sections from 2 cases of Q fever, the authors made the following observations:

1. The primary lesion, or eschar, is considered to be provoked by the combined action of the secretion of the larval mite and the inoculated rickettsiae. It is suggested that the absence of the eschar in certain instances of scrub typhus may be due to variations in cutaneous immunity.

2. Interstitial pneumonitis of a marked degree is common in scrub typhus in contrast with epidemic typhus and Rocky Mountain spotted fever. The histologic picture of the interstitial pneumonitis of scrub typhus is indistinguishable from that of Q fever, rheumatic fever, toxoplasmosis, and viral pneumonia.

3. It is concluded that the amount of hepatic damage as noted histologically does not warrant the presumption that hypoproteinemia is due to hepatic insufficiency.

4. Early, acute, diffuse glomerulonephritis is common in scrub typhus, epidemic typhus, and Rocky Mountain spotted fever. The indirect role of the rickettsiae in the pathogenesis of the glomerulonephritis is indicated.

5. The focal encephalitis or nodule of scrub typhus is qualitatively similar to that of epidemic typhus and is in contrast to the "microinfarct" of Rocky Mountain spotted fever. The nodules of scrub typhus and epidemic typhus are practically limited to the gray matter, whereas the encephalitis of spotted fever involves the white matter preponderantly.

6. Contrary to the generally held impression, there is a sparsity of histologically evident vascular damage in scrub typhus. Arteritis is exceedingly slight in scrub typhus in contrast with epidemic typhus and Rocky Mountain spotted fever. Accordingly, it is suggested that the designation "diffuse vasculitis" when applied to scrub typhus represents an oversimplification not justified by the morphologic evidence.

7. It is concluded that the peripheral circulatory failure in patients with rickettsial diseases is a complex phenomenon which cannot be explained solely on the basis of

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[34] See footnotes 5, p. 115; and 26, p. 125.

[35] Allen, A. C., and Spitz, S.: A Comparative Study of the Pathology of Scrub Typhus (Tsutsugamushi Disease) and Other Rickettsial Diseases. Am. J. Path. 21: 603-681, July 1945.

morphologic damage of vessels. The contributory role of the adrenal gland in the circulatory failure is suggested.

8. The evidence of lymphoblastic origin for the cells characterizing the interstitial infiltrate is presented. The identification of the large "basophilic macrophage" with the "acute splenic tumor cell" is suggested and the evidence pointing toward the association of these cells with an allergic response is given.

Finally, Allen and Spitz proposed a much broader pathological concept of the rickettsioses than that generally held at the time of their studies, as follows:

From the pathologic point of view, the rickettsioses have long been regarded as a form of diffuse vascular disease. Surely, this impression is almost inescapable after a study of epidemic typhus and spotted fever. However, the histology of scrub typhus may perhaps warrant a change in the direction of emphasis. Although focal, more or less bland thrombophlebitis in scrub typhus is not uncommon, actual arteritis occurs rarely, and, in our series, was never of the fibrinoid variety seen in louse-borne or tick-borne typhus. Moreover, the arteritis of scrub typhus does not seem to be a lesion *sui generis*, but, rather, appears to be secondary to an extension of the periarterial infiltrate into the wall. This interpretation was made previously by Kouwenaar. Yet, notwithstanding the disparity in the histologic evidences of vascular damage, there are basic clinical, etiologic, and, in many respects, immunologic similarities between scrub typhus and the other rickettsioses. Therefore, perhaps, a re-evaluation of the significance of the pathologic changes is in order. A close analogy to this problem is found in a nonrickettsial disease—acute disseminated lupus erythematosus (Libman-Sacks disease). The prominence of the degeneration of vessels in many organs led initially to the concept that this entity was a diffuse vascular disease. However, further studies prompted a broader concept; namely, that disseminated lupus erythematosus was in effect a disturbance of collagen, be it of a vessel, a cardiac valve, or a serous membrane. Moreover, the histologic and clinical pictures were such as to suggest a hyperergic reaction. The analogy may be extended by reference to periarteritis nodosa and to the arteritis that follows administration of sulfonamides. In other words, in the over-all view of the pathologist, the more remote, possibly hyperergic effects of the rickettsiae—the effects of the adrenal gland, on the glomeruli, and on the production of interstitial inflammation—assume more importance than the direct damage wrought by the localization of the rickettsiae.

LABORATORY AIDS IN DIAGNOSIS

The Weil-Felix reaction.—In 1929, Fletcher, Lesslar, and Lewthwaite,[36] while studying two forms of tropical typhus, discovered a serological difference which proved to be of considerable diagnostic value. They found that sera obtained from cases of rural typhus agglutinated in high dilution suspensions of the Kingsbury (K) strain of *Proteus*, in contrast to sera in urban typhus cases, which agglutinated the *Proteus* OX–19 micro-organisms. Subsequent studies showed the rural form to be the miteborne scrub typhus and the urban form to be murine (fleaborne) typhus.

During World War II, the Weil-Felix reaction was extensively employed in the laboratories of U.S. Army medical installations. Observations at the Virus and Rickettsial Diseases Laboratory, Army Medical Center, Washing-

[36] Fletcher, W., Lesslar, J. E., and Lewthwaite, R.: The Aetiology of the Tsutsugamushi Disease and Tropical Typhus in the Federated Malay States. Tr. Roy. Soc. Trop. Med. & Hyg. 23: 57–70, June 1929.

ton, D.C., clearly indicated the *Proteus* OX–K agglutination was not elicited by sera from other rickettsial diseases, and was, therefore, a valuable diagnostic aid for scrub typhus.[37]

Meanwhile, Zarafonetis,[38] working in the Cairo laboratory of the U.S.A. Typhus Commission, carried out a series of studies in typhus-vaccinated individuals to determine what serological effects may result from vaccination alone. Only one instance of OX–K agglutination was found, and there was no change in titer following booster vaccination. He concluded that typhus vaccination did not cause an increase in OX–K antibodies.

Proteus OX–K agglutination tests were also performed on serial blood specimens from 104 acutely febrile patients who had been previously vaccinated with Cox-type epidemic typhus vaccine. No anamnestic reactions were detected in these studies.

The final phase of these observations was concerned with the serological findings in typhus fever patients who developed their illness despite prior vaccination with Cox-type epidemic typhus vaccine.[39] Again, such patients were found not to develop agglutinins for suspensions of *Proteus* OX–K.

Thus, there appeared to be no need to modify the previously held interpretation of rising OX–K titers, that this finding was essentially specific for scrub typhus. However, in tests on sera from 51 cases of louseborne relapsing fever, Zarafonetis, Ingraham, and Berry[40] found that all patients had *Proteus* OX–K titers of 1:40 or more in at least one serum specimen. The titers ranged from 1:40 to 1:2,560. These workers suggested, therefore, that "since there is considerable overlapping in the geographic distribution of tsutsugamushi disease and louseborne relapsing fever, it becomes necessary to interpret Weil-Felix OX–K results with caution, particularly when atypical cases of either disease are in question."

Complement fixation tests.—At the outset and well into World War II, the Weil-Felix *Proteus* OX–K agglutination test was the only available serological test of value in the diagnosis of scrub typhus. It was fortunate that this nonrickettsial antigen appeared to be specific for scrub typhus with the single exception of louseborne relapsing fever that has been noted. In view of important progress in the development of specific rickettsial antigens for use in complement fixation and agglutination tests for other rickettsial diseases, it was anticipated that similarly successful results would follow with

[37] Plotz, H., Wertman, K., and Bennett, B. L.: The Serological Pattern in Epidemic Typhus Fever. II. The Weil-Felix Reaction. Division of Virus and Rickettsial Diseases, Army Medical School, Army Medical Center, Washington, D.C., 1944. [Official record.]

[38] (1) Zarafonetis, C. J. D.: Serologic Studies in Typhus-Vaccinated Individuals. I. The Effect of a Stimulating Dose of Typhus Vaccine on the Weil-Felix and Complement-Fixing Antibodies. J. Immunol. 51: 365-374, November 1945. (2) Zarafonetis, C. J. D.: Serologic Studies in Typhus-Vaccinated Individuals. II. The Effect of Non-Typhus Fevers on the Weil-Felix and Complement-Fixing Antibodies. J. Immunol. 51: 375-388, December 1945.

[39] Zarafonetis, C. J. D., Ecke, R. S., Yeomans, A., Murray, E. S., and Snyder, J. C.: Serologic Studies in Typhus-Vaccinated Individuals. III. Weil-Felix and Complement-Fixation Findings in Epidemic Typhus Fever Occurring in the Vaccinated. J. Immunol. 53: 15-30, May 1946.

[40] Zarafonetis, C. J. D., Ingraham, H. S., and Berry, J. F.: Weil-Felix and Typhus Complement-Fixation Tests in Relapsing Fever, With Special Reference to *B. proteus* OX-K Agglutination. J. Immunol. 52: 189-199, March 1946.

scrub typhus antigens. Bengtson,[41] at the National Institute of Health, U.S. Public Health Service, was the first to prepare satisfactory complement fixing antigens from infected eggs by a technique similar to that used for epidemic typhus. Additional experience, however, revealed that there were significant antigenic differences between various strains of *R. tsutsugamushi*. Because of these differences, diagnostic complement fixation tests on human sera require the use of several antigens prepared from different strains of *R. tsutsugamushi*. Thus, while the complement fixation test became available for scrub typhus, its use was limited essentially to research laboratories during World War II.

Isolation and identification of strains.—Diagnosis of scrub typhus by isolation of strains is, of course, absolute in contrast to the presumptive nature of serological tests. Isolation of strains is also desirable for laboratory comparison of immunity relationships between strains, for possible vaccine production, and for the preparation of antigens for serological tests. In addition, strains may be used in the laboratory evaluation of chemotherapeutic agents proposed for the treatment of scrub typhus. To these ends, therefore, strain isolations were carried out by several groups of workers in World War II and returned to adequately equipped laboratories for pertinent study.[42]

Prior to these efforts, attempts to isolate and serially transmit tsutsugamushi disease in laboratory animals gave negative results in the hands of many investigators. Japanese workers had been successful with rabbits, using intraocular injections. Mice were later found to be readily susceptible but were, unfortunately, not available for use in the field laboratories. Guinea pigs were susceptible to many tsutsugamushi strains, but apparently not to others. This was the situation in January 1944, when the Imphal, Ceylon, and Calcutta strains of scrub typhus were received in the Cairo, Egypt, laboratory of the U.S.A. Typhus Commission. These strains had been maintained at the district laboratory in Calcutta and at the Haffkine Institute in Bombay, India, by British workers and were forwarded to Brig. Gen. Leon A. Fox, Field Director, U.S.A. Typhus Commission, by Lt. Col. M. H. P. Sayers, RAMC. The strains were received in rabbits, infected intraocularly, and were maintained for several passages in rabbits. The infectivity of these strains for two desert rodents, namely, *Gerbillus pyramidum* and *Gerbillus gerbillus*, was then tested.[43] They were found to be highly susceptible to infection with *R. tsutsugamushi* and were, therefore, a suitable substitute in the absence of a supply of white mice. Since these rodents were plentiful, it

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41 Bengtson, I.A.: Complement Fixation in Tsutsugamushi Disease (Scrub Typhus). Pub. Health Rep. 61: 895-900, 14 June 1946.

42 (1) See footnote 1, p. 111; and 13, p. 121. (2) Philip, C. B., Woodward, T. E., and Sullivan, R. R.: Tsutsugamushi Disease (Scrub or Mite-Borne Typhus) in the Philippine Islands During American Reoccupation in 1944-45. Am. J. Trop. Med. 26: 229-242, March 1946. (3) Letter, Lt. Col. M. H. P. Sayers, R.A.M.C., Assistant Director of Pathology, 14th Army, Calcutta, India, to Brig. Gen. L. A. Fox, U.S.A. Typhus Commission, Cairo, Egypt, 4 Jan. 1944.

43 Zarafonetis, C. J. D.: The Susceptibility of the Rodents, *Gerbillus pyramidum* and *Gerbillus gerbillus*, to Experimental Tsutsugamushi Infection (Scrub Typhus). Proc. Soc. Exper. Biol. & Med. 59: 113-116, June 1945.

was possible to accelerate a number of studies in scrub typhus at the U.S.A. Typhus Commission laboratories at Myitkyina as well as in Cairo.

Growth of the etiological agent of scrub typhus in the yolk sac of developing chick embryos was accomplished by a number of workers.[44] This was an important method of experimental vaccine and antigen production.

SPECIFIC TREATMENT

The treatment of scrub typhus includes both general and specific measures. The general supportive measures consist of nursing care, diet, maintenance of fluid and electrolyte balance, and the management of complicating diseases or conditions. These aspects of therapy have been adequately indicated in the reports that have been cited.[45] Here, consideration will be limited to specific measures, such as the use of immune serum, antibiotics, and chemotherapy.

Serotherapy.—Hyperimmune rabbit serum was found to reduce the mortality of experimental scrub typhus in mice.[46] Human convalescent serum, however, was without effect on the clinical course of scrub typhus even when given during the first week of illness.[47] Since there are wide differences in the antigenic pattern of various strains of *R. tsutsugamushi*,[48] it may be that only homologous antiserum would be effective therapeutically.

Antibiotics.—Although penicillin and streptomycin proved to be valuable for certain complicating bacterial infections, these antibiotics had no significant specific effect on the etiological agent of scrub typhus. Since the war, the newer broad-spectrum antibiotics have been used with signal success in rickettsial infections.

Chemotherapy.—In a report to the Division of Medical Sciences, National Research Council, dated 26 December 1942, Drs. John C. Snyder, J. Maier, and C. Russell Anderson, first demonstrated an antirickettsial effect of PABA (para-aminobenzoic acid) in mice experimentally infected with murine (flea-borne) typhus. This led to extensive clinical and laboratory studies and to experimental trials of PABA in animals infected with *R. tsutsugamushi*. Gerbilles proved to be of great value in this connection. Snyder and Zarafonetis,[49] and Murray with these authors[50] demonstrated conclusively that,

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44 (1) See footnote 39, p. 134. (2) Bengtson, I. A.: Apparent Serological Heterogeneity Among Strains of Tsutsugamushi Disease (Scrub Typhus). Pub. Health Rep. 60: 1483–1488, 14 Dec. 1945. (3) Lewthwaite, R., and O'Connor J. L.: Prophylactic Vaccine Against the Tsutsugamushi Disease. Second Report on an Attempt to Prepare a Vaccine From Hens' Eggs Experimentally Infected. Virus Laboratory, Commonwealth Serum Laboratories, Melbourne, Australia, 1943.

45 See footnotes 1, p. 111; 9, p. 118; and 32, p. 128.

46 Topping, N. H.: Tsutsugamushi Disease (Scrub Typhus); The Effects of Immune Rabbit Serum in Experimentally Infected Mice. Pub. Health Rep. 60: 1215–1220, 12 Oct. 1945.

47 (1) See footnote 9, p. 118.. (2) Hay, C. P.: Scrub Typhus at Port "X." J. Roy. Nav. M. Serv. 30: 127–135, July 1944.

48 See footnote 44 (2).

49 Snyder, J. C., and Zarafonetis, C. J. D.: Effects of Para-Aminobenzoic Acid in Experimental Tsutsugamushi Disease (Scrub Typhus). Proc. Soc. Exper. Biol. & Med. 60: 115–117, October 1945.

50 Murray, E. S., Zarafonetis, C. J. D., and Snyder, J. C.: Further Report on Effect of Para-Aminobenzoic Acid in Experimental Tsutsugamushi Disease (Scrub Typhus). Proc. Soc. Exper. Biol. & Med. 60: 80–84, October 1945.

properly administered, PABA significantly reduced the mortality of experimental scrub typhus in gerbilles. PABA was effective against strains of *R. tsutsugamushi* that had come from widely separated regions including India, Ceylon, and New Guinea. On the basis of their observations, these workers strongly recommended a clinical trial of PABA therapy in human beings.

Such an opportunity presented itself to Tierney,[51] of the Cairo Unit of the U.S.A. Typhus Commission, in 1945. Working at the 20th General Hospital, in Ledo, Tierney carried out a controlled study on 18 patients with scrub typhus. He administered sufficiently large doses to obtain adequate blood concentrations of PABA and found that the treated patients had fewer complications and shorter fever than a comparable group of untreated subjects.

Although there are now improved means of administering large doses of PABA,[52] and PABA has itself been supplanted by the newer antibiotics as the treatment of choice in scrub typhus, these early studies were of great significance to those concerned with the scrub typhus problem. Lack of an effective vaccine, the insidious vector, the widespread distribution, and a significant mortality rate, all made scrub typhus an important medical problem affecting morale in the field. Furthermore, several prominent investigators succumbed to infections acquired during the course of laboratory investigations with *R. tsutsugamushi.* The search for an effective therapeutic agent for scrub typhus during World War II was stimulated by an awareness of these factors.

Immunization.—Information regarding the degree and duration of immunity following an attack of scrub typhus was fragmentary, even at the close of World War II. From the available data, it appeared that a strong and lasting immunity was induced by the disease, and considerable support was added to this belief by animal studies in several laboratories.[53] Indeed, these observations indicated that animals experimentally infected with one strain of *R. tsutsugamushi* are resistant for some months, at least, to inoculation with both homologous and heterologous strains. Studies in progress at the end of hostilities, however, revealed that a number of strains of *R. tsutsugamushi* had important antigenic differences as judged from cross-neutralization tests [54] and toxic neutralization tests,[55] as well as from study of the com-

[51] Tierney, N. A.: Effect of Para-Aminobenzoic Acid in Tsutsugamushi Disease. J.A.M.A. 131: 280–285, 25 May 1946.

[52] Zarafonetis, C. J. D.: Clinical Use of Para-Aminobenzoic Acid. Texas J. Med. 49: 666–672, September 1953.

[53] (1) See footnotes 1, p. 111; and 13, p. 121. (2) Bell, E. J., and Plotz, H.: Infection and Immunity Following the Intracutaneous Inoculation of Scrub Typhus. Proc. Soc. Exper. Biol. & Med. 59: 143–144, June 1945. (3) Zarafonetis, C. J. D., Snyder, J. C., and Murray, E. S.: Immunity Following Para-Aminobenzoic Acid Therapy in Experimental Tsutsugamushi Disease (Scrub Typhus). Proc. Soc. Exper. Biol. & Med. 61: 240–242, March 1946.

[54] Bell, E. J., Bennett, B. L., and Whitman, L.: Antigenic Differences Between Strains of Scrub Typhus as Demonstrated by Cross-Neutralization Tests. Proc. Soc. Exper. Biol. & Med. 62: 134–137, June 1946.

[55] Smadel, J. E., Jackson, E. B., Bennett, B. L., and Rights, F. L.: A Toxic Substance Associated With the Gilliam Strain of *R. orientalis.* Proc. Soc. Exper. Biol. & Med. 62: 138–140, June 1946.

plement fixation antigen.[56] From the observations and from efforts to produce an effective vaccine, it became evident that much remained to be learned regarding the immune response to the various scrub typhus strains.

Vaccine studies.—In view of the apparent immunity conferred by an attack of scrub typhus in man and confirmed in the animal work just noted, it was hoped that a satisfactory vaccine could be developed for scrub typhus as had been done for epidemic typhus. Several laboratories turned their attention to this problem. Fulton [57] at the National Institute for Medical Research in London prepared vaccines from the lungs of infected mice and cotton rats. He found some protection was afforded by intraperitoneal vaccination to intraperitoneal challenge. Similar observations were made by Smadel, Rights, and Jackson [58] at the Virus Division of the 1st Medical General Laboratory, 814th Hospital Center, Paris, France, and by Plotz, Bennett, and Reagan [59] at the Medical Department Professional Service Schools, Washington, D.C. The subcutaneous administration of these vaccines induced no resistance to infection.

Vaccine suspensions were also prepared from infected yolk sacs of developing chick embryos.[60] However, these preparations failed to confer immunity in a wide series of tests. It appears that the ether-extraction method, which was so valuable in the production of epidemic typhus vaccine, had some inexplicably deleterious effect when applied to suspensions of *R. tsutsugamushi.*

POSTWAR STUDIES

Immunity.—In the period immediately following the war, important work was done on unsettled problems bearing on prophylaxis and treatment. In studies conducted by Smadel and his associates at the Army Medical Department Research and Graduate School, Washington, D.C.,[61] it was found, briefly that in human volunteers immunity to the homologous strain of *R. tsutsugamushi* persisted for at least 1 year, and in some for longer periods. In contrast, resistance to heterologous strains of *R. tsutsugamushi* was of a transient nature. Even within a month after inoculation with one strain, an appreciable number of persons became ill following injection with a heterologous strain. By the end of a year, all were again susceptible to heterologous

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56 See footnote 44 (2), p. 136.

57 Fulton, F.: Methods For the Study of Mite Typhus—A Progress Report. National Inst. Med. Res., Hampstead, London, 21 June 1944.

58 Smadel, J. E., Rights, F. L., and Jackson, E. B.: Scrub Typhus Vaccines Prepared From Formalinized Suspensions of Tissues of White and Cotton Rats. Report dated 19 June 1945, Headquarters, First Medical General Laboratory, 814th Hospital Center, U.S. Army.

59 Plotz, H., Bennett, B. L., and Reagan, R. L.: Preparation of an Inactivated Tissue Culture Scrub Typhus Vaccine. Proc. Soc. Exper. Biol. & Med. 61: 313-317, March 1946.

60 See footnotes 44 (3), p. 136; and 59.

61 (1) Smadel, J. E., Ley, H. L., Jr., Diercks, F. H., and Traub, R.: Immunity in Scrub Typhus: Resistance to Induced Reinfection. Arch. Path. 50: 847-861, December 1950. (2) Smadel, J. E., Ley, H. L., Jr., Diercks, F. H., Paterson, P. Y., Wisseman, C. L., Jr., and Traub, R.: Immunization Against Scrub Typhus: Duration of Immunity in Volunteers Following Combined Living Vaccine and Chemoprophylaxis. Am. J. Trop. Med. 1: 87-99, January 1952.

infection. During the period of waning immunity, the disease which resulted from the heterologous strain was modified from the classical picture. Indeed, the illness observed in tests shortly after recovery was so mild that it would probably not have been recognized as scrub typhus if rickettsemia had not been demonstrated. On the other hand, the disease which resulted when the individuals were tested after 1 year generally presented the typical picture of scrub typhus.

Of further interest is the observation that only about 40 percent of the subjects who developed illness following reinoculation with scrub typhus after 1 year displayed a significant (fourfold) rise in titer of *Proteus* OX–K agglutinins.

Treatment.—In postwar studies, dramatic results in treatment of scrub typhus and other rickettsial infections were achieved with broad-spectrum antibiotics, such as Chloromycetin (chloramphenicol), Aureomycin (chlortetracycline), and Terramycin (oxytetracycline).[62] A program making use of these for chemoprophylaxis under special circumstances would not prevent infection but would prevent clinical illness. Field trials suggest that, if prophylactic medication is continued for 4 weeks or longer after exposure, it is unlikely that signs of scrub typhus will appear after the drug is discontinued.[63]

Vaccines are still (1957) in the experimental stage, but, in view of the immunity factors discussed, it is not anticipated that effective protection will be afforded in this manner.

SUMMARY

During World War II, scrub typhus was found to be endemic in foci distributed throughout a large triangular region of Asia and the Pacific which lies between Japan, India, and Australia. Outbreaks are more common in types of terrain that provide suitable cover for reservoir hosts as well as moisture conditions favorable to the growth and activity of the vector mites. Wild mice and rats and jungle tree squirrels are known to be naturally infected with *R. tsutsugamushi*. Larval mites of the genus *Trombicula* transmit the disease from animal to animal or from animal to man. Since infection of the mites can be transovarially acquired, the vector also serves as an important natural reservoir of scrub typhus.

[62] (1) Smadel, J. E., Woodward, T. E., Ley, H. L., Jr., and Lewthwaite, R.: Chloramphenicol (Chloromycetin) in the Treatment of Tsutsugamushi Disease (Scrub Typhus). J. Clin. Investigation 28: 1196–1215, September (pt. 2) 1949. (2) Smadel, J. E., Jackson, E. B., and Ley, H. L., Jr.: Terramycin as a Rickettsiostatic Agent and Its Usefulness in Patients With Scrub Typhus. Ann. New York Acad. Sc. 53: 375–384, 15 Sept. 1950. (3) Prezyna, A. P., Teh-Ling, C., Tsu-Lin, W., Dougherty, W. J., and Bond, H. B.: Treatment of Scrub Typhus in the Pescadores Islands With Chloramphenicol, Aureomycin, and Terramycin. Am. J. Trop. Med. 3: 608–614, July 1954.

[63] Smadel, J. E., Traub, R., Frick, L. P., Diercks, F. H., and Bailey, C. A.: Chloramphenicol (Chloromycetin) in the Chemoprophylaxis of Scrub Typhus (Tsutsugamushi Disease). III. Suppression of Overt Disease by Prophylactic Regimens of Four-Week Duration. Am. J. Hyg. 51: 216–228, March 1950.

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The desert rodents, *G. pyramidum* and *G. gerbillus*, were shown to be susceptible to infection with scrub typhus and were valuable experimental animals in studies on this disease during World War II.

Clinical picture.—After an incubation period of from 6 to 18 days, the illness begins abruptly with chilly sensations or rigors, followed by fever, headache, malaise, and anorexia. The face is flushed, and there is conjunctival injection. A primary lesion or eschar is present in nearly all cases at the time of onset. It may have been present for as long as 5 days earlier, and usually persists throughout the active phase of the disease. The eschar represents the site of infection by the mite. Occasional patients exhibit more than one eschar. This lesion may be up to 1.0 cm. in diameter and consists of a central tough black scab surrounded by a slightly elevated dull red areola (fig. 9). In moist areas of the body, such as the axilla, groin, and scrotum, the scab is often lacking, and the lesion appears as a shallow punched-out ulcer. It is neither painful nor pruritic. There is often regional or generalized lymphadenitis. The spleen may become palpable. The fever rises in stepwise fashion, reaching 102° to 105° F. by the end of the first week. It usually remains elevated until the third week at which time it subsides by lysis. As the disease passes into its second week, the general symptoms are increased except in mild cases.

On about the fifth to the eighth day, a dull red macular eruption appears first on the trunk (fig. 10) and later spreads to the arms, legs, and face. It varies in intensity and extent and lasts from 1 to 10 days. Nonproductive cough is common, and in severe cases, bronchitis and pneumonia may appear. Roentgen examination of the chest may reveal changes similar to those of primary atypical pneumonia. Indeed, pathological studies suggest that these findings represent a rickettsial pneumonitis. Hypotension, tachycardia, and cyanosis may occur at the height of the disease and are attributed more to peripheral vascular collapse than to heart failure.

The clinical features presented by the scrub typhus patient reflect the histopathology of the disease, which is basically a disseminated, focal vasculitis and perivasculitis especially of the vessels of the skin, lungs, heart, and brain.

Leukocyte counts are usually within normal limits, but a moderate leukocytosis may develop during the second week of illness.

Diagnosis.—The typical case of scrub typhus is readily diagnosed on the clinical findings. Prior to the appearance of the cutaneous eruption, however, early diagnosis depends upon finding an eschar, since dengue, relapsing fever, malaria, infectious hepatitis, typhoid fever, epidemic typhus, and murine typhus exhibit many of the same clinical features.

The diagnosis may be confirmed by serological tests. A significant rise in titer in the Weil-Felix *Proteus* OX–K agglutination test differentiates scrub typhus from other rickettsial infections. However, patients with relapsing fever also develop OX–K agglutinins. Complement fixation tests



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FIGURE 9. Eschar on ankle in tsutsugamushi disease.



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FIGURE 10.—The rash of tsutsugamushi disease is a faint macular one, frequently transient in nature.

with purified suspensions of *R. tsutsugamushi* may be useful in the diagnosis, but the sera must be tested with antigens prepared from several different strains of the micro-organism. This is necessary because there are important antigenic differences between various strains. Although recovery and identification of the micro-organism proves the diagnosis, it is not feasible for routine use.

Natural course.—After the first week, the subsequent course of scrub typhus may be relatively mild, with a total febrile period of 12 to 14 days, or it may be moderately severe with signs of encephalitis and pneumonitis and fever up to 3 weeks. In severe cases, patients are febrile for about 3 weeks, have signs of pneumonitis, encephalitis, and often of circulatory collapse and myocarditis. Thromboses and cerebral or gastrointestinal hemorrhage may occur. Death is not infrequent in severe cases. However, the mortality of untreated cases varies from 1 to 25 percent or more in different series. The death rate rises sharply after the age of 40. There is evidence that the course of scrub typhus is likely to be more severe in men who have been under the strains of combat or have lacked early treatment.

Recovery from scrub typhus is ultimately complete. Many patients, however, have a prolonged convalescence and present a picture of neurocirculatory asthenia with sleeplessness, tremulousness, lack of ability to concentrate, easy fatigability, excessive sweating, palpitation, dyspnea, and sense of intrathoracic pressure.

Relapse is rare in cases that have run their natural course.

Following an attack of scrub typhus, immunity to the homologous strain appears to persist for at least a year. Resistance to heterologous strains of *R. tsutsugamushi*, however, is transient.

Therapy.—The patient should be placed at bed rest, avoid overexertion, and receive frequent small feedings and adequate fluid intake. Specific therapy should be instituted as early as possible. Scrub typhus during World War II was found responsive to high doses of PABA (best administered as a 10-percent chilled aqueous solution of the sodium or, preferably, the potassium salt);[64] since World War II, chemotherapy has been successful.

Prophylaxis.—Prevention of scrub typhus in areas where it is endemic is difficult, at best, and may be impossible under combat conditions. When feasible, preventive measures should include appropriate clearing and oiling of campsites to change the ecology of the area so that it is unfavorable to rodents and mites. Impregnation of clothing with dimethyl phthalate, or with an emulsion of benzyl benzoate and dibutyl phthalate, affords considerable individual protection as mites which come in contact with treated cloth are killed. In view of the immunity factors that have been referred to, it is not anticipated that effective protection will be afforded by the development of a vaccine.

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64 See footnote 52, p. 137.

CHAPTER VII

The Typhus Fevers

Chris J. D. Zarafonetis, M.D.

Part I. Epidemic Typhus

Epidemic typhus fever is an acute febrile disease [illegible]ection with *Rickettsia prowazeki*. It is a louseborne infection and is characterized clinically by sustained high fever, headache, malaise, and later an exanthem. It has been known under many names including exanthematous typhus, jail fever, ship fever, war fever, camp fever, Old World typhus, Fleckfieber (German), typhus exanthematiqué (French), el tabardillo (Spanish), and hassin chifusu (Japanese).

For centuries, epidemics of typhus fever have been associated with war, revolution, and famine, and have indeed, in the past, been a factor affecting the outcome of wars. The death toll exacted in some epidemics has been estimated in millions of lives. An account of the historical role of typhus fever has been written by Zinsser,[1] and Strong and his associates[2] have documented the great Serbian epidemic of 1915.

Clinically, no differentiation was made between typhoid fever and louseborne typhus fever until 1837. In that year, Gerhard, in Philadelphia, noted differences between the two, and was the first to call attention to the presence of typhus in the New World. That typhus is transmitted by *Pediculus humanus* var. *corporis* was discovered by Nicolle, Comte, and Conseil in 1909. The causative agent, *R. prowazeki*, was first described in 1916 by Da Rocha-Lima. For many years, it was believed that there was only one form of typhus fever, but it is now known that the epidemic louseborne form and the endemic fleaborne typhus are caused by different micro-organisms. It has been further shown that epidemic typhus fever may be recrudescent in a patient years after the original illness, in the disorder known as Brill's disease.

EPIDEMIOLOGY

Typhus fever exists in many parts of the world, with important foci in the Balkans, North Africa, China, and Mexico, and it presumably occurs in Poland, the U.S.S.R., and elsewhere. Man is the reservoir of epidemic typhus (p. 201). It is transmitted from man to man by body lice which become infected by feeding upon typhus patients during the febrile period. The rickettsiae multiply in the cells lining the intestinal tract of the louse. A week

1 Zinsser, Hans: Rats, Lice and History. New York: Little, Brown and Co., 1934.

2 Strong, Richard P., Shattuck, George C., Sellards, A. W., Zinsser, Hans, and Hopkins, J. Gardner: Typhus Fever With Particular Reference to the Serbian Epidemic. Cambridge, Mass.: Harvard University Press, 1920.

or 10 days after the vector has become infected, the parasitized cells rupture and large numbers of rickettsiae begin to appear in its feces. Lice prefer the normal temperature of the body and usually remain close to their human host. If the temperature is raised by fever or lowered by death, however, they will migrate to a new host. Here, lice suck blood and defecate as they feed, and when the site of the bite is scratched, the infected feces are rubbed into the skin. This appears to be the principal means by which the infection is passed from man to man. It is also possible to acquire it by crushing an infected louse upon the skin, or by having dried infected feces come into contact with the conjunctivae or the mucous membranes of the respiratory tract. Infection with typhus rickettsiae is eventually fatal to the louse.

Conditions that predispose to louse infestation naturally predispose to epidemics of typhus fever. The scene is set by crowding, inadequate housing, lack of bathing facilities, lack of fuel, and such continued cold weather that people wear their garments for long periods of time. Once louse infestation is prevalent, introduction of the infection, either from a patient with typhus or from one with the recrudescent (Brill's) disease, may set off an epidemic. The chaotic effects of war and famine, shifting populations, and the breakdown of orderly processes of government contribute conditions that favor spread of the infection.

At the beginning of World War II, it was evident that American troops would be exposed to typhus fever in most oversea theaters of operations. It was recognized that few physicians in the Armed Forces would have had experience with a disease conspicuous by its absence from the continental United States. Against this background, the United States of America Typhus Commission was created by the Secretary of War on 22 October 1942 in response to a staff-approved recommendation of The Surgeon General, initiated by Col. (later Brig. Gen.) James S. Simmons, MC, and established by Executive order of President Roosevelt on 24 December 1942.[3] The order provided for a joint attack upon the problems of the disease by the Army, the Navy, and the U.S. Public Health Service. As a result of the comprehensive mandates and authorizations of this broadly conceived Executive order, and of the impetus given to the work by the director, field director, and members of the Commission, typhus investigation was intensified, leading to the development of specific diagnostic procedures, improved methods of treatment, the large-scale production of a potent vaccine, and excellent louse-control measures. For detailed information regarding epidemiology and preventive measures, and a history of the Typhus Commission, the reader is referred to the brilliant account by Stanhope Bayne-Jones in another volume in the history of the Medical Department in World War II.[4]

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[3] Bayne-Jones, S.: The United States of America Typhus Commission. Army M. Bull. No. 68, pp. 4–15, July 1943.

[4] Bayne-Jones, Stanhope: Typhus Fevers. *In* Medical Department, United States Army. Preventive Medicine in World War II. Volume VII. Communicable Diseases: Arthropodborne Diseases Other Than Malaria. [In preparation.]

CLINICAL EXPERIENCE

Although epidemic typhus fever posed a constant threat to soldiers in several oversea theaters (table 13), the remarkable fact remains, however, that there were only 104 cases in U.S. forces and not a single death (table 14). Bayne-Jones has described the extraordinarily effective measures that were implemented for the protection of U.S. troops in areas where epidemics of louseborne typhus were prevalent among civilian populations. As one result of this splendid record, there was no opportunity for medical officers in various station and general hospitals to accumulate extensive experience with epidemic typhus in our troops. The clinical studies to be recorded here are, therefore, largely those performed by members of the Typhus Commission, and are generally concerned with the disease as observed in civilian populations. This is in contrast to the observations on scrub typhus in the several excellent studies made by other medical officers and units in addition to the contributions of the U.S.A. Typhus Commission (pp. 116–138).

TABLE 13.—*Epidemic typhus in French North Africa, Egypt, and Iran, 1930–44*

Year	Number of reported cases		
	French North Africa	Egypt	Iran [1]
1930	529	288	[2]
1931	930	265	1, 167
1932	965	2, 298	1, 544
1933	1, 671	7, 865	327
1934	1, 456	7, 536	1, 212
1935	1, 977	3, 151	619
1936	2, 182	2, 757	202
1937	8, 921	2, 083	116
1938	11, 377	2, 867	16
1939	9, 353	4, 239	86
1940	3, 547	4, 135	397
1941	21, 726	9, 324	245
1942	77, 335	23, 941	1, 102
1943	27, 340	40, 084	12, 885
1944	6, 226	18, 533	6, 436

[1] Data pertain to cities only.

[2] Data are not available.

Source: (1) Stowman, K.: Typhus During the War. Epidemiol. Inform. Bull. 1 (7): 289–310, 30 Apr. 1945. (2) *Current Reports on the Prevalence of Certain Diseases.* Epidemiol. Inform. Bull. 1 (7): 311–326, 30 Apr. 1945.

The Disease in Nonvaccinated Individuals

The Typhus Commission established special study facilities at the Cairo Fever Hospital, Egypt, in March 1943.[5] The Ministry of Health of the

[5] Minutes, Conference on Typhus, National Research Council, 22 June 1944.

Egyptian Government provided the study ward and space for laboratories. During the 1943 and 1944 seasons, 159 patients with typhus fever were admitted to this ward, and numerous other cases were observed in other wards of the hospital. With three exceptions, all of the patients studied on the Commission ward were males. Their ages ranged from 10 to 70 years, the great majority falling in the 21- to 35-year age group. In general, the patients were selected as early in the disease as possible. The majority were admitted between the 5th and 10th day of illness. A few were admitted on the first day of disease, while in four instances, patients were actually under observation before the onset of illness.

TABLE 14.—*Incidence of epidemic typhus fever (louseborne) in the U.S. Army, by area and year, 1942–45*

[Preliminary data based on sample tabulations of individual medical records]

[Rate expressed as number of cases per annum per 1,000 average strength]

Area	1942–45		1942		1943		1944		1945	
	Number of cases	*Rate*	*Number of cases*	*Rate*	*Number of cases*	*Rate*	*Number of cases*	*Rate*	*Number of cases*	*Rate*
Continental United States	.....	0.00	.....	0.00	.....	0.00	.....	0.00	.....	0.00
Overseas:										
Europe	10	0.00	.....	0.00	.....	0.00	.....	0.00	10	0.00
Mediterranean [1]	16	.01	1	.04	12	.03	3	0	.....	0
Middle East	14	.10	1	.17	8	.15	.....	0	5	.12
China-Burma-India	63	.14	1	.11	25	.63	12	.07	25	.11
Southwest Pacific	.....	0	.....	0	.....	0	.....	0	.....	0
Central and South Pacific	1	0	.....	0	1	0	.....	0	.....	0
North America [2]	.....	0	.....	0	.....	0	.....	0	.....	0
Latin America	.....	0	.....	0	.....	0	.....	0	.....	0
Total overseas	104	0.01	3	0.01	46	0.03	15	0.00	40	0.01
Total Army	104	0.00	3	0.00	46	0.01	15	0.00	40	0.01

[1] Includes North Africa.

[2] Includes Alaska and Iceland.

This section of the chapter will be restricted to a consideration of the unvaccinated subjects who received no special therapy beyond supportive measures. There were 64 such "untreated" cases studied on the Commission ward. The severity of the clinical course of the disease was estimated for each patient after discharge from the hospital. The principal factors which influenced the estimation of severity were the intensity of subjective symptoms (headache, generalized bodily aches and pains, tinnitus, deafness), the degree of prostration, the extent of neurological involvement (mental dullness, stupor, coma, incontinence of urine and feces, signs referable to the central nervous system), the severity of cardiovascular involvement (hypotension, tachycardia, peripheral vascular failure, myocardial damage), and, finally, occurrence of urinary retention, oliguria, nitrogen retention, bronchopneu-

monia, otitis media, parotitis, furunculosis, and gangrene.[6] On the basis of these criteria, these cases were grouped as follows:

B. Cases with minimal signs and symptoms, yet definitely diagnosed as typhus on clinical evidence.

C. Cases of moderate severity, showing slight prostration, involvement of the central nervous system, cardiovascular changes, or mild complications.

D. Severe typhus cases with pronounced prostration, involvement of the central nervous system, cardiovascular changes, or serious complications.

E. Cases of such severe illness that at some point in the clinical course a fatal outcome was expected.

F. Fatal cases.

Of the 64 cases of "untreated" typhus fever, there were 2 in the B group, 14 in C, 26 in D, 7 in E, and 15 in F, the fatal cases, a mortality of 23 percent. It was of particular interest that 33 (52 percent) of the patients developed nitrogen retention (nonprotein nitrogen over 45 mg. percent) during the disease. All 15 fatal cases were in this group, and no patient died who throughout his illness had normal concentration of nonprotein nitrogen in the blood.

The following case histories, taken from a Commission publication,[7] will serve to illustrate typhus fever classified as severe (E or F):

Case 1 (classified as E; severe, with neurological involvement).—The patient, male, aged 25, was admitted on the sixth day of disease with headache as his chief complaint. Temperature 40.7° C. p.r. Pulse 108. Respirations 36. Blood pressure 126 mm. Hg systolic and 66 mm. diastolic. Weight 121 pounds. The patient was moderately well developed and nourished. He appeared mentally clear and not acutely ill. There was no tinnitus or deafness. The skin was dark; no evidence of a typhus rash was seen. The conjunctivae were negative. The tongue was white coated and moist. The chest was clear to percussion and auscultation. Examination of the heart showed nothing remarkable.

Laboratory data on admission.—Hemoglobin 83 percent ($CuSO_4$); erythrocytes 4,500,000; leukocytes 7,550, with 81 percent polymorphonuclear cells. Urine was amber in color, cloudy, reaction acid, and specific gravity 1.028. A few squamous epithelial cells, 1–2 granular casts per low-power field, 1–3 leukocytes per high-power field were seen in the centrifugated sediment. The concentration of nonprotein nitrogen was 46 mg. per 100 cc. of blood. The plasma proteins were 6.8 gm. per 100 cc.

Hospital course (chart 4).—Throughout the first week of hospitalization the patient's fever remained high and the rash appeared, with intense conjunctival injection and the development of petechiae in the left conjunctival sac. The patient, actively delirious, became very talkative and attempted to get out of bed. Intake by mouth continued satisfactorily until the 12th day of disease when subcutaneous injections of 5 percent dextrose in saline and normal saline became necessary for the next 12 days.

On the 13th day he became more stuporous and then semicomatose. He lay with half-opened eyes, breathing quietly. Facial grimaces and grinding of the teeth were noted. Fluid intake by mouth practically ceased. He was put on constant bladder drainage on this day because of urinary retention. His condition remained much the same to the

[6] Yeomans, A., Snyder, J. C., Murray, E. S., Zarafonetis, C. J. D., and Ecke, R. S.: The Therapeutic Effect of Para-Aminobenzoic Acid in Louse Borne Typhus Fever. J.A.M.A. 126: 349–356, 7 Oct. 1944.

[7] Yeomans, A., Snyder, J. C., Murray, E. S., Ecke, R. S., and Zarafonetis, C. J. D.: Azotemia in Typhus Fever. Ann. Int. Med. 23: 711–753, November 1945.

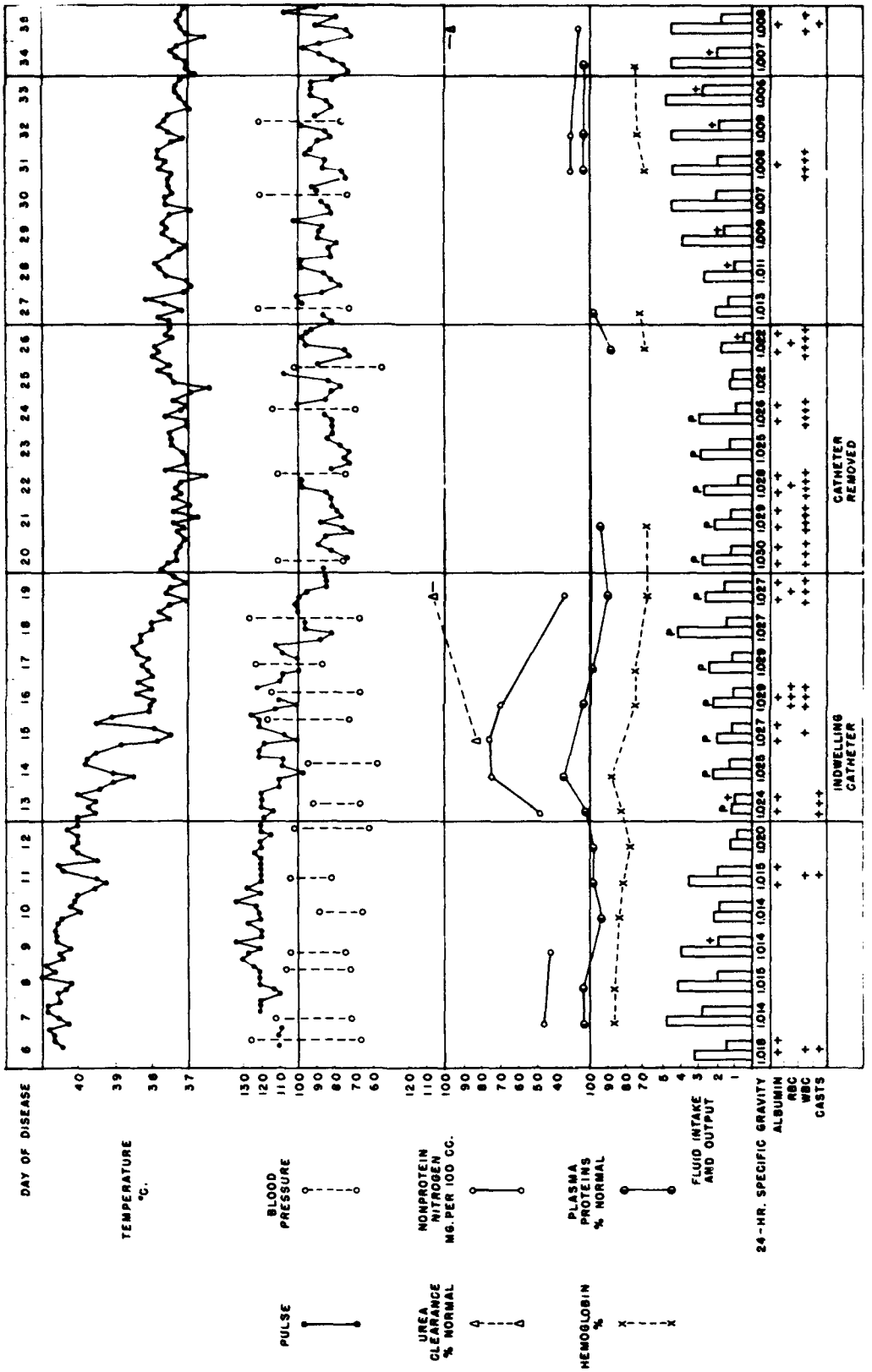


CHART 4.—*Clinical and laboratory findings in patient with "E" severity typhus fever*

Source: Yeomans, A., Snyder, J. C., Murray, E. S., Ecke, R. S., and Zarafonetis, C. J. D.: Azotemia in Typhus Fever. Ann. Int. Med. 23: 711–753, November 1945.

17th day of disease. The rash gradually faded out during this period and the conjunctival suffusion disappeared.

On the 17th day slight improvement was noted in his mental state. He stared about the ward, his mouth open in a wide grimace. When spoken to he replied in a series of unintelligible whining sounds. There was no indication that he recognized people. The rash was no longer visible.

In the next 2 days he was able to obey simple commands. It was evident that he was almost totally deaf. On the 20th day his temperature reached normal levels. Examination showed hyperactive knee jerks and ankle jerks but normal plantar response. An area of skin necrosis appeared over the coccyx.

On the 22d day the catheter was removed. When he was spoken to it was obvious that he was attempting to reply, but he could not articulate and the facial expressions were similar to those of a crying baby.

The area of necrosis over the lower back continued to enlarge. The patient was placed in a chair on the 24th day. A low-grade fever continued. He was by that time able to eat solid food and the oral fluid intake gradually increased.

On the 27th day the patient was found to have not only hyperactive knee and ankle jerks but a bilateral positive Babinski reaction. Voluntary motion of the extremities was uncoordinated.

From this time onward improvement in his general condition was steady but slow. The ability to stand and walk unassisted returned before the ability to form words. At the time of discharge 68 days after the onset of the disease, the lesion over the coccyx was healed. Speech was slow, expressionless, and labored. Hyperactive reflexes were still present in the lower extremities, but the positive Babinski phenomenon had disappeared.

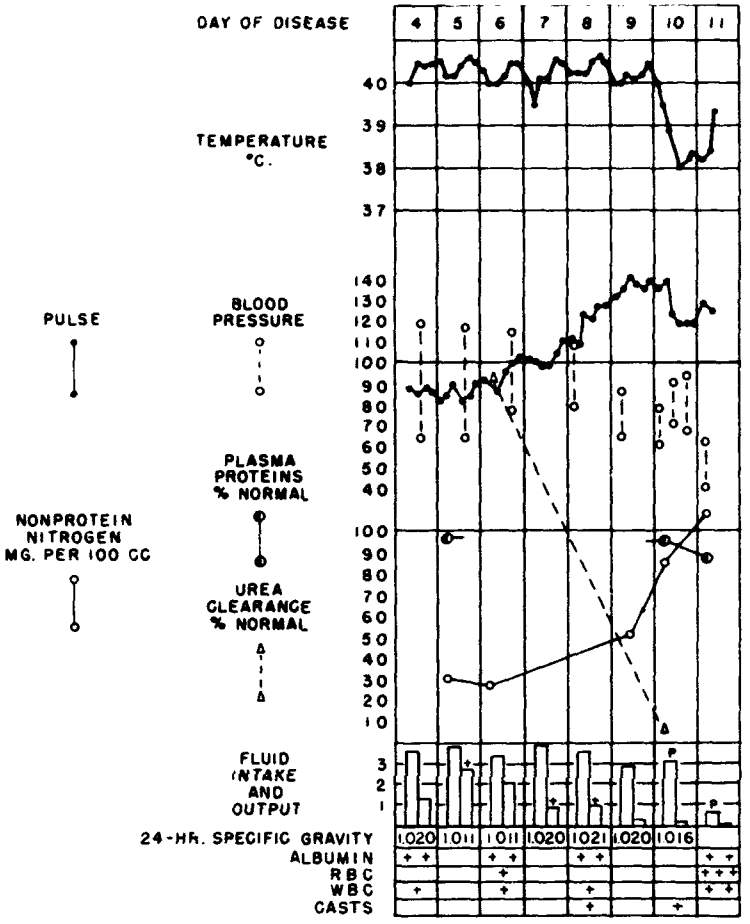
On followup examinations during the next 4 months the patient showed progressive improvement. Mentally he appeared alert. There was no residual deafness. The reflexes in the lower extremities remained hyperactive, however, and speech was still slow, labored, and monotonous in tone. Examination of the urine showed normal concentrating power, no albumin, and a negative urine sediment. The anemia that had developed during the disease was no longer present.

Case 2 (classified as F; fatal, with post mortem).—The patient, male, aged 30, was admitted on the fourth day of disease complaining chiefly of headache. Temperature 40.0° C. p.r. Pulse 88. Respirations 36. Blood pressure 118 mm. Hg systolic and 64 mm. diastolic. Weight 116 pounds. The patient appeared moderately ill, mentally clear, with rapid respirations, and no cough. A few poorly defined maculopapular lesions were noted over the chest, abdomen, and arms. The conjunctivae appeared moderately injected. The tongue was moist. A few crepitant rales were heard in the right midlung field posteriorly. Examination of the heart showed nothing remarkable. The spleen was enlarged, but not tender; its tip was felt 7 cm. below the costal margin. The liver was not palpable, but was found enlarged 3 cm. below the costal margin by percussion.

Laboratory data on admission.—Hemoglobin 72 percent ($CuSO_4$); red cells 4,110,000; white cells 4,300, with 76 percent polymorphonuclear cells. Urine was amber in color, reaction acid, specific gravity 1.023, albumin 2+, 8–10 white cells per high-power field, and an occasional granular cast was seen in the centrifugated sediment. The concentration of nonprotein nitrogen was 30 mg. per 100 cc. of blood. The plasma proteins were 6.5 gm. per 100 cc.

Hospital course (chart 5).—In spite of frequent sponging, the patient continued to run a high fever from the fourth to the ninth day of disease. On the fifth day, the maculopapular rash increased, but the macules were still scanty and poorly defined. On the sixth day, the patient became disoriented. On the eighth day he was quite drowsy and vomited twice. His general condition, however, appeared satisfactory. On the ninth day he became semicomatose. The pulse rate had increased to between 130–140 beats per

CHART 5.—*Clinical and laboratory findings in a fatal case of epidemic typhus fever*



minute. The blood pressure fell. The respirations were rapid. The neck was resistant to passive flexion. Examination of the heart and lungs was negative. Spinal puncture revealed an initial pressure of 90 mm., and the dynamics were normal. Seven cubic centimeters of spinal fluid was withdrawn. The final pressure was 60 mm. The cell count of the spinal fluid was 5 per cu. mm. The Pandy test was negative. An electrocardiogram showed low voltage of the QRS complexes. The patient was given 1,000 cc. of 5 percent dextrose in saline subcutaneously.

On the morning of the 10th day, his general condition had become critical. There was oliguria; the blood pressure was low; the heart rate still rapid. He was given 100 cc. of concentrated human albumin intravenously. Subcutaneous injections of 0.5 gm. of caffeine with sodium benzoate were given every 2 hours. Slight improvement in his general condition was noted throughout the day, with a decrease in heart rate and a rise in blood pressure. The state of oliguria continued, however. There was no increase in the rash from the fifth day.

On the morning of the 11th day the patient had a generalized convulsive seizure and died.

At post mortem examination 1 hour after death, the interesting findings were as follows: The rash, which had been scanty throughout his illness, was not discernible. No gross areas of pneumonitis were noted in the right lung; the left lung was crepitant throughout; the bronchi appeared normal. The heart weighed 330 gm.; no gross abnormalities were seen on the epicardial or endocardial surfaces; the ventricular walls were

of normal thickness; the coronary arteries were patent. The liver weighed 2,430 gm.; its was grayish in color, firm and rubbery in consistency; the surface was lobulated, with numerous white fibrotic areas in the depressions between the lobules. On section the cut surface was gray. Areas of dense fibrosis were present throughout the organ. Numerous adult schistosomes were obtained from the blood in the portal vein. The spleen weighed 770 gm.; the surface was mottled with numerous white, bluish, and reddish areas, some of which were firm in consistency. On section the pulp was firm and deep red in color. The surface patches extended a few millimeters into the spleen substance and appeared to be demarcated by a narrow zone of hemorrhage.

The right kidney weighed 210 gm.; there were a few pinpoint hemorrhagic spots on its surface. On section the cortex appeared to be slightly pale. The kidney pelvis appeared normal. The left kidney weighed 190 gm., with findings similar to those seen in the right kidney. The ureters appeared normal and patent. The mucosa of the bladder was of light yellowish tint and was thickened. Small areas of hemorrhage were present in the region of the trigone.

The mucosa of the large intestine and rectum showed mottled areas of bluish and brownish discoloration. There were numerous elevated nodules of 0.5 to 0.7 cm. in diameter with smooth surfaces. These were not pedunculated and were pale green to blue black in color. The findings in the liver, bladder, and large bowel were secondary to an extensive Schistosoma infection.

Pathological physiology.—The observation that there was a high incidence of nitrogen retention in their typhus cases led Yeomans and his associates to analyze the factors that might contribute to its development. They reasoned that—

* * * a fundamental consideration * * * [is] that the caloric and protein intake of nearly all typhus patients is grossly insufficient. There is good reason to believe that the destruction of the body tissues must be considerable * * *. In order to prevent the accumulation of nitrogenous metabolites in the blood, the excretion of an adequate [amount] of urine * * * is necessary. In the presence of a greatly increased protein catabolism it is apparent that dehydration with a diminished output of urine will have considerable effect upon the degree of azotemia observed.

Another factor * * * in the more critically ill patients * * * is the onset of renal insufficiency, most often associated with a rapid fall in blood pressure. [This] * * * is of serious prognostic import. In our experience * * * the majority of these patients died with evidences of overwhelming rickettsial infection or complicating conditions, such as pneumonia, [but] a rapid diminution in kidney function was almost without exception the first indication that the patient would probably succumb to the disease. The * * * renal insufficiency itself was of more significance than a fall in blood pressure, since at times such a fall was not observed or occurred in the absence of renal failure. At present we have no evidence to indicate that the loss of renal function observed in these critically ill patients was due to other than extrarenal factors.

In French Morocco, Maj. Theodore E. Woodward, MC, of the U.S.A. Typhus Commission collaborated with Maj. (later Lt. Col.) Edward F. Bland, MC, 6th General Hospital, in a study of 30 native patients with typhus fever.[8] They draw a composite picture of the pathological physiology of severe typhus as follows:

The patient is acutely ill and very toxic, with a significantly low arterial tension and a labile pulse. Usually, unless actively supported, the patient becomes dehydrated, the

[8] Woodward, T. E., and Bland, E. F.: Clinical Observations in Typhus Fever, With Special Reference to the Cardiovascular System. J.A.M.A. 126: 287–293, 30 Sept. 1944.

red cells decrease and plasma proteins fall with a considerable loss of the albumin fraction, indicating a reduced colloidal osmotic pressure. All factors indicate a drop of blood volume with the pattern of hypoproteinemia, hypochloremia, and hemodilution without blood destruction. The unstable circulation results in lowered glomerular filtration pressure, and hence oliguria and anuria occur. The kidney, partially damaged by the specific pathologic condition and called on to eliminate an increased amount of nitrogenous waste, is unable to function normally unless adequately supported by fluids. Lowered blood volume means less adequate filling of the heart during diastole and hence lowered cardiac output. Each beat of the heart is less efficient. The use of cardiac stimulants under these conditions is ineffectual, but when the volume of the blood is restored the organ can operate more efficiently.

Woodward and Bland note that the typhus lesion had been demonstrated by Wolback and his associates in heart muscle, in the kidney, and in almost every other organ. However, the degree of both cardiac and renal changes they observed was not disproportionate to the pathological changes occurring elsewhere, and from their clinical studies it appears "unlikely that cardiac failure as such is often a significant factor in the outcome of the fatal case." In treatment, they advocate "general supportive measures to increase the circulating blood volume."

Metabolic studies.—These observations focused attention on the azotemia and hypochloremia associated with a high proportion of typhus fever cases. Since a better understanding of electrolytes and protein metabolism was deemed essential for appropriate supportive treatment, Tierney and Yeomans [9] undertook metabolic studies in cases of typhus fever on the Commission ward in Cairo.

Tierney and Yeomans determined the carbon dioxide content and the chlorides of the serum in 34 cases. They found the serum chlorides to be low in 62 percent of the patients during the first 2 weeks of disease, but the serum carbon dioxide content was appreciably reduced in only four cases. Explanation was sought for the low serum chlorides in the early stages of typhus. The diets of these patients were probably poor in salt prior to hospitalization, but this was not an important factor since there was no conspicuous chloride deficit in patients admitted to the Commission ward with relapsing fever and typhoid fever. Perspiration was not a factor, as it was rarely observed; indeed, failure to perspire was noted in typhus patients not only in the dry climate of Egypt but also in moist climates. The salt was not lost in the urine, for urinary excretion was in relation to the concentration of chlorides in the serum; when serum chlorides fell below normal levels, the urinary chlorides diminished markedly. The fact that the serum chlorides returned to normal spontaneously in spite of a poor salt intake was taken as evidence that the salt was not lost by the body and that the lowered chloride concentration was therefore due to expansion of the extracellular fluid volume. During the early stage of typhus, the patients frequently have nonpitting

[9] Tierney, N. A., and Yeomans, A.: Metabolic Studies in Louse-Borne Typhus; Observations on Serum Electrolyte Pattern, Serum Protein Partition, and Nitrogen Balance. J. Clin. Investigation 25: 822–837, November 1946.

edema; in the later stage, shortly before defervescence there is often a fairly marked diuresis. These observations are in keeping with the suggestion that early in the disease there is an increase in extracellular fluids, which would lower the serum chlorides, and later in the disease there is a loss of extracellular fluid by diuresis with a resultant increase in serum chlorides. The pH was normal in all of the patients except one who had renal failure and acidosis. The total base was also normal in all but one of the subjects studied. In all instances, the quantity of undetermined acid anions was increased in the majority of cases equaling that found in severe metabolic acidosis.

The total serum proteins were normal in approximately 75 percent of the patients, but the majority showed a depression of the albumin fraction and a very striking elevation of the globulin fraction to over 40 percent in the average case. An electrophoretic analysis [10] of sera obtained from a severely ill patient on the ward of the Cairo Unit of the Typhus Commission showed that the relative proportion of albumin and the albumin to globulin ratio was markedly reduced on the fourth day of fever and through convalescence. The alpha and beta globulins were practically unaffected, but the gamma globulin was strikingly increased on the fourth day and was even higher in convalescence.

Nitrogen balance studies were performed on 21 subjects. Eight of the patients were given high-protein, high-caloric diets; ten, low-protein, low-caloric diets; and three were given a combination of these. It was found that there was no relationship between nitrogen output and intake or between protein destruction and azotemia. A high-protein, high-caloric diet decreased nitrogen wastage and loss of body weight during the acute phase of typhus. Indeed, positive nitrogen balance was achieved in five of the patients studied.

Dietary management.—From these and other observations on the Commission ward, the following recommendations were made with regard to management of diet, electrolytes, and fluids in the typhus patient:

1. A liquid diet high in protein and calories should be given. With diligent nursing, the average patient will ingest at least 90 gm. of protein and 2,500 calories a day. If the patient is too ill to take the diet, Amigen may be given intravenously.

2. The routine administration of large amounts of sodium chloride without determining the serum chlorides should be avoided. By including in the diet or in the parenteral fluids 4 to 6 gm. of sodium chloride a day, the serum chlorides should be kept within normal limits and good state of hydration achieved. Usually, the fluid intake should be maintained between 3 and 4 liters daily.

3. The urine output should be at least 1 liter a day, and preferably 1.5 liters. As a marked drop in the urine output is an ominous sign, particularly

[10] Dole, V. P., Yeomans, A., and Tierney, N. A.: Electrophoretic Changes in the Serum Protein Pattern of a Patient With Typhus Fever. J. Clin. Investigation 26: 298–300, March 1947.

if associated with a fall in the arterial blood pressure, plasma or blood transfusions in such cases are urgently required.

4. In cases of shock or impending shock, plasma or blood transfusions are indicated. The effect of plasma or blood transfusions on hypoalbuminemia is transient. In order to produce any significant change, very large amounts of plasma over a period of days would be required.

5. Acid salts, such as ammonium chloride, are obviously contraindicated because of the increase in undetermined acids in the blood.

Epidemic in Italy.—The clinical observations that have been described were carried out under relatively ideal conditions. However, members of the Typhus Commission and other physicians of the U.S. Army Medical Service saw thousands of additional cases under epidemic, and often chaotic, conditions throughout Europe and the Far East. In a few instances, efforts were made to glean clinical data even under the most adverse of circumstances. These reports will be mentioned briefly.

The epidemic at Naples, Italy, during 1943 and 1944 involved some 1,407 cases within the city itself and 492 cases outside Naples. Vigorous application of delousing measures quickly brought this epidemic under control. This historic accomplishment has been detailed by Bayne-Jones.[11] Here, it will suffice to note that the case fatality rate was about 22.6 percent. Woodward,[12] in his report of the activities of the flying squadron group for typhus control outside Naples, recorded brief observations on 257 cases diagnosed on the basis of clinical findings, along with serological tests. Of interest was the relatively high incidence in children, many of whom showed a characteristic rash and were moderately ill.

Observations in concentration camps.—Maj. William A. Davis, MC, while serving as liaison officer from the U.S.A. Typhus Commission to the 21st Army Group, recorded the typhus fever epidemic that occurred at the Belsen Concentration Camp, Belsen, Germany.[13] This camp was taken by the British Second Army on 15 April 1945. Among the 61,000 inhabitants, there was widespread suffering from starvation, typhus, dysentery, tuberculosis, and other diseases. Typhus had been prevalent in the camp for 4 months, and there were approximately 3,500 cases at the time of liberation. Practically all of the internees were heavily infested with lice.

Davis stated that the appraisal and diagnosis of cases was peculiarly difficult in this group. Prostration, semistupor, dehydration, loss of weight, weakness, tremors, and a petechial rash, which are considered characteristic of typhus, were so common in the starving, louse-infected people that he

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[11] Bayne-Jones, Stanhope: Epidemic Typhus in the Mediterranean Area During World War II. *In* Rickettsial Diseases of Man. Washington: American Association for the Advancement of Science, 1948, pp. 1–15.

[12] Woodward, T. E.: History of Flying Squadron Group for Typhus Control in Italy. To the Field Director, U.S.A. Typhus Commission, 29 Mar. 1944.

[13] Davis, W. A.: Typhus at Belsen. I. Control of the Typhus Epidemic. Am. J. Hyg. 46: 66–83, July 1947.

found these signs of little value. The rash was mild; very few had ecchymoses, and the usual finding was a scattered petechial exanthem best seen after the patient had been washed. Gangrene was common, particularly dry gangrene of the toes. Pleuritic pain was a frequent complaint in the post-typhus period. About 30 cases of parotitis were observed that required incision. Several patients had polyneuritic leg pains, which may have reflected vitamin B deficiency exacerbated by the increased metabolic demands of fever. No statistics were available on the death rate from typhus fever at Belsen.

Epidemic typhus fever was also prevalent at the Dachau Concentration Camp, Dachau, Germany, when it was liberated by the Seventh U.S. Army on 29 April 1945. Measures were taken to control the disease, and special clinical facilities were made available to the Typhus Commission [14] at the 116th Evacuation Hospital. On 16 May 1945, six nurses from the 59th Evacuation Hospital arrived and began their duties on the Typhus Commission Service, a special ward of 64 beds which admitted patients, 83 in all, until 30 May 1945. The ward was closed 9 June 1945. Most of these patients were treated with PABA (para-aminobenzoic acid) or serum therapy as discussed in the section on treatment (p. 192). Here, the data on 121 untreated controls are of interest. These were male patients of various nationalities in the wards of the 116th Evacuation Hospital, ranging in age from 17 to 58 years, with an average age of 28 years. The duration of fever averaged 16.2 days in this group.

Of particular interest is the observation that the typhus fever encountered at Dachau was clinically a mild disease. Fewer patients were seen with full-blown rashes than in other epidemics. There appeared to be less prostration and delirium, and a shorter convalescence. To be sure, there were some severe cases, but not so many as had been expected. The comparative mildness of the disease was surprising to Commission observers who had seen patients in Cairo, Naples, and elsewhere, and had anticipated that the general debility of the Dachau patients would predispose them to a considerable mortality. The fatality rate from typhus for all Dachau hospitals during 9 May to 9 June 1945, was, however, 9.1 percent.

Additional serious outbreaks of typhus fever were encountered among civilian populations in other areas of the European Theater of Operations, U.S. Army,[15] and in Japan and Korea,[16] but circumstances prevented the undertaking of special clinical studies during these epidemics.

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[14] A Report on the Activities of the U.S.A. Typhus Commission at the Dachau Concentration Camp, Dachau, Germany, 10 May 1945-10 June 1945, prepared by Lt. Comdr. A. Yeomans, MC; Maj. C. J. D. Zarafonetis, MC; Capt. D. H. Clement, MC; Lt. Comdr. R. A. Phillips, MC, USNR; and Lt. Col. J. C. Snyder, MC.

[15] Gordon, John E.: Louse-Borne Typhus Fever in the European Theater of Operations, U.S. Army, 1945. *In* Rickettsial Diseases of Man. Washington: American Association for the Advancement of Science, 1948, pp. 16–27.

[16] Scoville, Addison B., Jr.: Epidemic Typhus Fever in Japan and Korea. *In* Rickettsial Diseases of Man. Washington: American Association for the Advancement of Science, 1948, pp. 28–35.

The Disease in Vaccinated Individuals

The remarkable record of low morbidity with no fatalities from epidemic typhus fever in the U.S. Army during the war years, 1942–45, was achieved by taking adequate protective measures against the disease. One of the most important was the compulsory immunization of all soldiers going to areas where epidemic typhus was present or suspected. Accordingly, those few cases that did occur in troops, along with those encountered in certain special studies, offer an unusual opportunity to analyze the modifications of clinical course resulting from vaccination. The value of serological tests in the diagnosis of typhus in vaccinated individuals is implicit in the clinical material to be summarized, although particular consideration of these tests will be left for the section on laboratory methods (p. 179).

The Cox (U.S. Army) vaccine.—Early work by Da Rocha-Lima (1918) and Weigl (1920) suggested that killed suspensions of typhus-infected lice or infected louse feces could endow some immunity as vaccines. However, these and other methods advanced for vaccine preparation up to 1938 were not practical for large-scale production. It was a highly significant discovery, therefore, when Cox [17] demonstrated in 1938 that rickettsiae could be grown in the yolk sac of the developing chick embryo. Cox and Bell [18] soon prepared an epidemic typhus vaccine which consisted of a killed suspension of micro-organisms grown in yolk sacs and purified by centrifugation. Subsequent modifications included an ether-extraction technique devised by Craigie [19] and the incorporation of soluble antigen in the vaccine.[20] The resultant product was not only satisfactory from the standpoint of potency but was also feasible for commercial production. The final product used by the U.S. Army consisted of a 10-percent yolk-sac suspension of the Breinl strain of *R. prowazeki*, extracted with ether; it contained both killed micro-organisms and soluble substances. Up through 1943, the initial vaccination for U.S. Army personnel consisted of three injections of the vaccine, 1.0 cc. each, administered subcutaneously at intervals of 7 to 10 days, with stimulating doses given every 6 months in endemic areas. As the vaccine was improved in potency through improvement in production, the initial immunization series was reduced in mid-1944 to two doses of vaccine, with

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[17] Cox, H. R.: Use of Yolk Sac of Developing Chick Embryo as Medium for Growing Rickettsiae of Rocky Mountain Spotted Fever and Typhus Groups. Pub. Health Rep. 53: 2241-2247, 23 Dec. 1938.

[18] Cox, H. R., and Bell, E. J.: Epidemic and Endemic Typhus: Protective Value for Guinea Pigs of *Vaccines Prepared From Infected Tissues of Developing* Chick Embryo. Pub. Health Rep. 55: 110–115, 19 Jan. 1940.

[19] Craigie, J.: Application and Control of Ethyl-Ether-Water Interface Effects to the Separation of Rickettsiae From Yolk Sac Suspensions. Canad. J. Research, Sect. E. 23: 104-114, June 1945.

[20] (1) Plotz, H.: Report on the Testing of Four Different Typhus Vaccines in Guinea Pigs, 20 Mar. 1942, to Col. George R. Callender, MC, Director, Army Medical School, Army Medical Center, Washington, D.C. (2) Topping, N. H., and Shear, M. J.: Studies of Antigens in Infected Yolk Sacs. Pub. Health Rep. 59: 1671–1675, 29 Dec. 1944.

stimulating doses at the beginning and in the middle of the typhus season (1 November and 1 February in the Northern Hemisphere).[21]

As might be expected, a satisfactory field trial of vaccine of the Cox type was one of the principal objectives of the Typhus Commission when it was formed in 1942.[22] In January 1943, the field group of the Commission, with the cooperation of the Egyptian Ministry of Public Health, began a study on the effect of the vaccine in a large number of persons intimately exposed by their occupations to naturally acquired typhus fever. This study was continued through the epidemics of 1943 and 1944. The subjects were employees of the Cairo Fever Hospital at Abassia and the Embaba Hospital. Because of the exceptionally large numbers of patients with typhus being admitted to these hospitals, the hospital staff was unusually exposed to the infection, and in addition many of the employees lived in areas of the city where attack rates were high. Before 1943, these workers had not been vaccinated against typhus. During 1943 and 1944, vaccine of the Cox type was, accordingly, administered to all employees who desired it. Careful records were kept on more than 800 employees at Abassia and over 500 at Embaba. Most of those who contracted febrile illnesses, whether vaccinated or not, were seen by one or more of the Commission members. During the course of these two typhus seasons, a group of 61 postvaccination cases were observed.

Despite the mild course that distinguished many of these cases, Ecke and his associates[23] usually found it possible to recognize the disease on clinical grounds alone, and laboratory tests confirmed the diagnosis in almost every case. In some patients, however, the diagnosis of typhus was made only by a rise in titer in the Weil-Felix and complement fixation tests during illness or in early convalescence. The diagnostic significance of these laboratory aids had been worked out by Zarafonetis in studies of 100 known febrile illnesses other than typhus and 16 definite cases of postvaccination typhus. In brief, he found that, on the one hand, nontyphus febrile illnesses do not evoke high complement fixation titers in the sera of patients who have had multiple doses of vaccine of the Cox type. On the other hand, typhus infections regularly do stimulate high complement fixation titers in the sera of vaccinated patients. Similar results were usually obtained with the Weil-Felix test. So interpreted, these laboratory aids could be relied upon in those cases where the clinical evidence alone was inadequate for diagnosis, either because of inconspicuous symptoms or insufficient observation (p. 179).

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[21] Sadusk, J. F., Jr.: Typhus Fever in the United States Army Following Immunization: Incidence, Severity of the Disease, Modification of the Clinical Course, and Serologic Diagnosis. J.A.M.A. 133: 1192-1199, 19 Apr. 1947.

[22] See footnote 3, p. 144.

[23] Ecke, R. S., Gilliam, A. G., Snyder, J. C., Yeomans, A., Zarafonetis, C. J. D., and Murray, E. S. The Effect of Cox-Type Vaccine on Louse-Borne Typhus Fever; An Account of 61 Cases of Naturally Occurring Typhus Fever in Patients Who Had Previously Received One or More Injections of Cox-Type Vaccine. Am. J. Trop. Med. 25: 447-462, November 1945.

These postvaccination cases were arbitrarily classified in the categories devised for typhus in nonvaccinated persons (p. 145) with, in addition to B, C, D, E, and F groups, an A group for cases "so mild that a definite diagnosis of typhus on clinical evidence alone was not possible, the final diagnosis being made only with the aid of laboratory data." The cases were further grouped according to the amount of vaccine received and the interval between the last inoculation and the onset of illness.

The course of typhus fever in vaccinated Egyptians was recorded by the Typhus Commission observers, as follows:

Group 1 (three doses of vaccine at least 21 days prior to onset).—Clinical notes from the records of five patients who were thoroughly studied on the Commission ward illustrate some of the features of postvaccination typhus.

Case 1.—Three doses of vaccine, the last dose 39 days before onset. Male, aged 45 years. This patient had a severe chill the first day combined with frontal headache and, later, joint pains. Rash was moderate. His mild course was marked latterly by the development of bilateral costovertebral pain and microscopic hematuria. After 12 days of moderate elevation of temperature he continued to maintain a low-grade fever until the 21st day. (The importance of his hematuria in relation to typhus is not clear: Bilharzia infection is widespread in Egypt.) Clinical classification of severity: B.

Case 2.—Five doses of vaccine, the last dose 117 days before onset. Male, aged 26 years, Typhus Commission field worker. He had rather severe headache and malaise. The rash was fleeting but definite. With the history and the rash no difficulty was experienced in making the diagnosis, though the course was mild. Fever lasted 9 days. Clinical classification of severity: B.

Case 3.—Three doses of vaccine, the last dose 87 days before onset. The patient, male, aged 45 years, appeared to be at least 55. He was never especially ill during his course. He developed a tremor of his limbs, almost parkinsonian in character. This disappeared during convalescence. Fever lasted 12 days. Clinical classification of severity: B.

Case 4.—Three doses of vaccine, the last dose 103 days before onset. Male, aged 18 years. This case was a problem in diagnosis. Moderately ill; said he felt "weak," but had no specific complaint. There was nothing to be found but a very few fleeting macules requiring careful search. There was no conjunctival injection. Fever lasted 10 days. Clinical classification of severity: B.

Case 5.—Five doses of vaccine, the last dose 79 days before onset. An obese male, aged 33 years. He complained of generalized body pains, especially in the knees, and said he felt "feverish." He had severe headache. There was some tinnitus and slight deafness. His course was mild. Fever lasted 8 days. Clinical classification of severity: B.

The average duration of fever for all the patients in group 1 was 10½ days. The cases were classed as follows: 1 in A, 20 in B, 5 in C, none in D, E, or F. Fifteen of the patients were females, average age 22.7 years; 11 patients were males, average age 31.8 years.

Group 2 (two doses of vaccine at least 21 days prior to onset).—The seven patients in group 2 had an average duration of fever of 12 days. The cases were classed as follows: 4 in B, 3 in C. Four patients were females, average age 19 years. Three patients were males, average age 28 years.

Group 3 (one dose of vaccine at least 21 days prior to onset).—The 11 patients in group 3 had an average duration of fever of 12.7 days. The cases

were classed as follows: 2 in B, 8 in C, and 1 in D. Five patients were females, average age 21 years. Six patients were males, average age 34 years.

Group 4 (onset of typhus less than 12 days after first dose of vaccine). —There were 17 patients in group 4. The average duration of fever in the nonfatal cases was 15 days. The cases were classed as follows: 4 in B, 8 in C, 4 in D, and 1 in F. There were 12 females, average age 23.6, and 5 males, average age 27.8 years.

In discussing these results, Ecke and his coworkers pointed out that, before the vaccination program was undertaken, typhus fever among the employees of the Cairo Fever Hospital was characteristically severe. The relatively few employees who remained unvaccinated and contracted typhus during the study period were likewise severely stricken. By contrast, among those who had received two or more doses of Cox vaccine 21 days or more before the onset of illness (groups 1 and 2), there were no severely ill patients, that is, D, E, or F cases, whereas two-thirds of the unvaccinated patients in the same age groups fell into the severe groups, D, E, or F. (Compare with the 64 nonvaccinated cases summarized on p. 147.) On the basis of these observations, and insofar as attenuation of clinical course is concerned, it was postulated that adequate vaccination against typhus could be defined as two or more doses of Cox-type vaccine of standard potency administered more than 21 days before the onset of typhus.

On the basis of their observations during this study, Ecke and his coworkers recommended that vaccination be included in epidemic control programs.

Sadusk [24] consolidated much of the information regarding epidemic typhus fever that occurred in U.S. Army personnel subsequently to immunization. His report contains details of five cases, three in members of the Typhus Commission. These case histories will illustrate the course of typhus fever in vaccinated Americans and, at the same time, will serve as a reminder of the added health hazards to which medical officers are at times exposed in line of duty.

Case 1.—A 41-year-old male officer, member of the U.S.A. Typhus Commission, for almost a month before the onset of illness was engaged in typhus research work in Cairo, Egypt, together with the officer described in case 2. They were both daily exposed to infection with typhus by examining patients, picking infected lice off rabbits and patients, and handling and grinding infected louse feces for injecting into experimental animals. During the preceding 2 years, this officer had received a total of 22.0 cc. of vaccine in single 1.0 cc. doses. Five cubic centimeters of this vaccine was of an experimental lot and contained both epidemic and murine virus. The last dose of vaccine was given on 1 March 1944.

On 21 May 1944, the patient had a mild headache, general malaise, and felt feverish. Although the headache became more severe and the temperature ranged between 100.0° and 101.0° F. during the next 3 days, he continued his work. On the sixth day, 26 May,

[24] See footnote 21, p. 157.

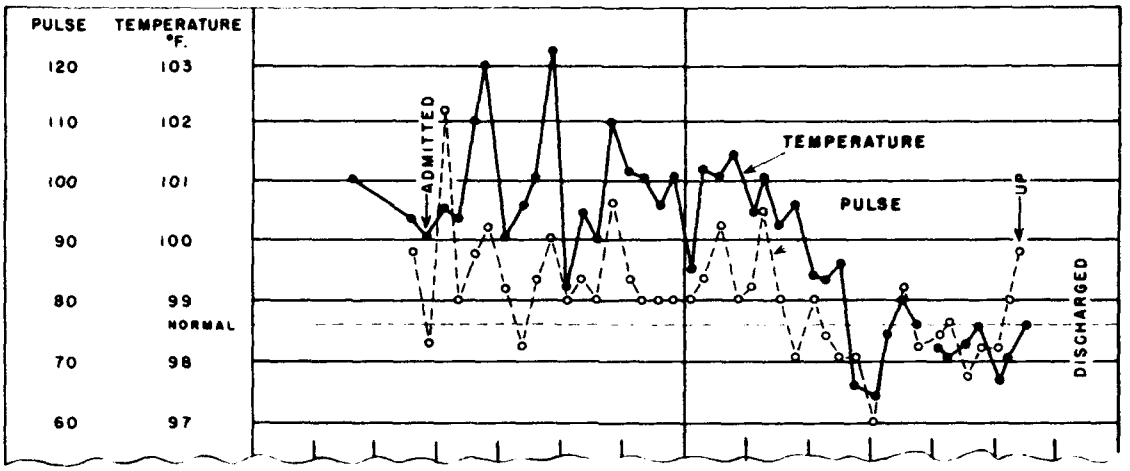
he took to his bed because of headache, fatigue, and malaise. Backache was marked. The next day he reported to a medical dispensary where physical examination revealed a few pink papules on the left palm and wrist, a temperature of 99.2° F., and a pulse rate of 100. The rash had disappeared by the following morning and except for a mild headache, anorexia, and sense of fatigue, the patient did well on bed rest in his quarters, reporting daily to the dispensary. He was afebrile by 27 May (7th day) and was permitted to remain out of bed on 31 May (11th day).

Prior to the onset of typhus, on 21 March and 4 April 1944, the Weil-Felix reaction was negative with both *Proteus* OX–19 and OX–2 antigens and the complement fixation titer was 1 : 8 with epidemic antigen and 1 : 4 with murine antigen. By the end of the first week of disease the *Proteus* OX–19 titer rose to 1 : 20, and in the second week it rose to 1 : 80. It reverted to negative in the fourth week. The complement fixation titer rose rapidly to a high of 1 : 1,024 in the second week. More than 2 years later, the complement fixation (with epidemic antigen) was still positive with a titer of 1 : 10.

Case 2.—A 35-year-old male officer, member of the U.S.A. Typhus Commission, was engaged in typhus research work in Cairo with the patient described in case 1, for a month prior to onset of illness. Although exposed daily, he recalled that he was dangerously exposed on 11 June 1944 when he assisted with the handling and grinding of infected louse feces in large amounts. During the period from 23 December 1941 to 10 October 1943, he received a total of 12.0 cc. of typhus vaccine in 1.0 cc. increments. On 22 November 1943 he received 1.0 cc. epidemic typhus vaccine and on 10 April an additional and final dose of 1.0 cc. of vaccine. Although the Weil-Felix reaction was negative with both *Proteus* OX–19 and *Proteus* OX–2 antigen, the complement fixation titer with epidemic antigen was 1 : 8, 3 days before and 11 days after the last dose of vaccine.

On 23 June 1944, the patient awakened in the morning with a mild but troublesome frontal headache which persisted through most of the day, and the following day recurred together with malaise and easy fatigability. His temperature was 101.0° F. As these symptoms persisted with an increase in both severity and extent of the headache, he was admitted to the hospital late in the afternoon of the next day, 25 June. The following day his temperature was 100.4° F., pulse rate was 80, respiratory rate 20, blood pressure was 106 systolic and 60 diastolic. Although he did not appear acutely ill, he complained of headache, chilly sensations, and nausea. Physical examination revealed only a marked injection of the scleral conjunctivae. Later in the afternoon his temperature rose to 102.0° F. and a diffuse macular eruption appeared over the anterior chest, arms, shoulders, and flanks with an erythematous blush that disappeared upon pressure. He continued that afternoon and night to have slight chills. By the next morning the rash had definitely faded but his headache, which was now generalized, became exceptionally severe. Chills continued, and he appeared quite ill. There were intermittent, drenching sweats, and he complained of severe backache and general malaise. The temperature rose to 103.2° F. that night with a pulse rate of only 90. The respiratory rate was normal. Although the temperature fell to 99.2° F. the following morning (28 June) and remained below 100.6° F. throughout the course of the day, severe headache, malaise, sweating, and occasional chills persisted. He vomited several times and on one occasion there was a transient amnesia. During the course of the next 2 days, these symptoms persisted but the temperature remained relatively low and the rash became increasingly less evident, and disappeared completely by 1 July. On 29 June the physician reported that the patient appeared to be disoriented for a brief period but this was not confirmed and was later denied by the patient. From 30 June on, there was rapid and progressive improvement, as illustrated in chart 6, with rapid fall in temperature by lysis, subsidence of headache, malaise, nausea, and vomiting, and rapid increase in serological titers for typhus fever. On 30 June, there was a left earache which disappeared within 48 hours without specific

CHART 6.—*Clinical course and early serological findings in a moderately severe case of epidemic typhus in a vaccinated individual*



DAY OF DISEASE		1	2	3	4	5	6	7	8	9	10	11	12	13	14
BLOOD PRESSURE					106/60	106/60	106/60		106/64	106/70	104/66		110/60	114/60	
RESPIRATORY RATE					20	20 20	20 20	22 20	20 22	22 18	20 18	20 20	18 18	20 20	
HEADACHE		+	±	++	+	+++	+++	+++	+	—	—	—	—	—	—
CHILL					+	+	+	—	—	—	—	—	—	—	—
RASH				—	++	+	+	±	±	—	—				
WBC X 1,000				6.3								5.6			
PROTEUS OX-19			—	—	—	—	—	—	1:20		1:80		1:160		1:640
COMPLEMENT FIXATION	EPIDEMIC		1:8	1:8	1:8	1:32	1:32	1:64	1:128		1:128		1:256		1:256
	MURINE		—	—	—	—	—	—	1:8		1:32		1:32		1:64

Source: Sadusk, J. F., Jr.: Typhus Fever in the United States Army Following Immunization; Incidence, Severity of the Disease, Modification of the Clinical Course, and Serologic Diagnosis. J.A.M.A. 133: 1192-1199, 19 Apr. 1947.

therapy. Temperature was normal by 3 July. On 5 July he was permitted out of bed and was discharged on the following day as an ambulatory patient.

During the course of the patient's stay in the hospital, there was no marked hypotension. On 25 June, the day of admission, the red cell count was 4,600,000, the hemoglobin was 95 percent, and the leukocyte count was said to be 6,300 with 45 percent stab cells, 33 percent polymorphonuclear neutrophils, 20 percent lymphocytes, and 2 percent monocytes. On 3 July the blood count was as follows: red cells 4,650,000, hemoglobin 95 percent, leukocytes 5,600 with 15 percent stab cells, 53 percent polymorphonuclear neutrophils, 18 percent lymphocytes, and 14 percent monocytes. Urine examination on 26 June was negative. It was clear amber and specific gravity was 1.010. Tests for albumin and sugar were negative.

Serological tests were performed daily during the acute phase of the disease. The Weil-Felix reaction with *Proteus* OX–19 antigen remained negative until the eighth day when it became positive in a titer of 1:20. It then rose rapidly reaching a top figure of 1:1,280 on the 19th day. It was still positive at 1:80 on the 124th day but when next checked, almost 2 years after the onset of the disease, it was found to be negative. Complement fixing antibodies began to rise by the end of the first week of disease, reaching a peak with epidemic antigen of 1:512 by the 19th day. The titer began to fall after the

31st day and when last checked almost 2 years later, the titer was still positive at 1:20. Specific rickettsial agglutinations were negative at that time. The temperature and pulse record, along with other pertinent findings during the acute phase of this patient's disease, are shown in chart 6.

Case 3.—A 36-year-old male officer, member of the U.S.A. Typhus Commission, was engaged in typhus control work in Hokkaido, Japan. On 10 November 1945, he was heavily exposed in the room of a Japanese hospital to dust containing suspended louse feces from the clothing of a patient with active typhus. From 17 February to 28 July 1944 he had received a total of 4.0 cc. of typhus vaccine in 1.0 cc. doses. On 9 May and 1 October 1945, he received additional 1.0 cc. doses of the vaccine. On 6 June and 4 August 1945, serology was as follows: Weil-Felix negative, complement fixation 1:10 with epidemic antigen and negative with murine antigen, and rickettsial agglutination 1:40 with epidemic antigen and negative with murine antigen.

On 22 November 1945, the patient experienced chilly sensations and generalized malaise. The following day headache, apathy, anorexia, and irritability appeared. These persisted during the next 2 days with chilliness, and although he felt feverish he did not take his temperature. On the fifth day, his temperature was 101.8° F., pulse rate was 88, and respiratory rate was 20. Headache became more severe and was predominately bitemporal. A persistent dry hacking cough set in and he vomited once. The next day, sixth day of disease, he refused hospital admission but finally took to bed in his quarters. Headache became excruciating in severity, temperature rose to 102.2° F., and nausea and cough persisted. Although the temperature rose to 103.8° F. the night of the seventh day and he became drowsy, there was suddenly a feeling of relative well being the following day with sudden resolution of fever by crisis and profuse sweats. He was afebrile by the 9th day, and was out of bed on the 10th day, and back to work on the 13th day, although he tired easily on exertion. The blood pressure remained normal throughout and there was no rash. The lungs were clear.

The leukocyte count on the seventh day was 5,000. On the 13th day complete blood count at an outpatient clinic showed 4,620,000 red cells, 90 percent hemoglobin, and 6,600 leukocytes with a differential of 64 percent segmented neutrophils, and 36 percent lymphocytes. On the 12th day, urine was negative except for a faint trace of albumin with a few leukocytes in the microscopic examination. These findings had disappeared by the following day. On the 21st day, electrocardiographic tracing was normal in all four leads. The heart rate was 84, the PR interval was 0.16 second, sinus rhythm was present, QRS complexes were 0.06 second, T waves were upright in all leads, and there were no ST changes.

The serological changes are given in detail in table 15. Briefly, Weil-Felix reaction became positive on the 7th day with a titer of 1:40 and reached as high as 1:80 by the 14th day. The complement fixation with epidemic antigen began to rise by the end of the first week, reached its peak at 1:1,280 at the end of the third week, and was still positive by the ninth month. Rickettsial agglutination did not rise until the second week but reached its peak at that time with a titer of 1:640 with epidemic antigen. It was still positive by the ninth month.

The pertinent serological data on the three cases just mentioned are given in table 15, and the essential clinical features of these and two other vaccinated cases are summarized in table 16. Of particular interest is the method of infection. In each instance, there was evidence to indicate inhalation or conjunctival absorption of infected louse feces.

TABLE 15.—*Serological findings and immunization record in three cases of epidemic typhus fever incurred subsequent to immunization with typhus fever vaccine*

Case	Typhus vaccine [1]		Date of serum specimen	Day of disease	Serological findings						
	Date	Amount (cc.)			Weil-Felix			Complement fixation		Rickettsial agglutination	
					OX-19	OX-2	OX-K	Epidemic	Murine	Epidemic	Murine
1	21 Feb. 1942-31 Jan. 1944.	[2] 21.0	21 Mar. 1944	−61	—	—	-------	1:8	1:4	--------	------
	1 Mar. 1944	1.0	4 Apr. 1944	−47	—	—	-------	1:8	1:4	--------	------
			27 May 1944	7	1:20	—	-------	1:256	1:128	--------	------
			31 May 1944	11	1:80	—	-------	1:1,024	1:256	--------	------
			6 June 1944	17	1:20	—	-------	1:512	1:128	--------	------
			10 June 1944	21	1:20	—	-------	1:512	1:256	--------	------
			13 June 1944	24	1:20	—	-------	1:512	1:256	--------	------
			17 June 1944	28	—	—	-------	1:512	1:128	--------	------
			21 June 1944	32	—	—	-------	1:512	1:128	--------	------
			24 June 1944	35	—	—	-------	1:512	1:128	--------	------
			28 June 1944	39	—	—	-------	1:512	1:128	--------	------
			4 July 1944	45	—	—	-------	1:256	1:128	--------	------
			23 July 1944	64	—	—	-------	1:256	1:64	--------	------
			3 Aug. 1944	75	—	—	-------	1:256	1:32	--------	------
			29 Aug. 1944	101	—	—	-------	1:64	1:16	--------	------
			16 Sept. 1944	119	—	—	-------	1:64	1:16	--------	------
			25 Sept. 1946	818	—	—	-------	1:10	—	--------	------
2	23 Dec. 1941-10 Oct. 1943.	12.0	7 Apr. 1944	−77	—	—	—	1:8	—	--------	------
	22 Nov. 1943	1.0	21 Apr. 1944	−63	—	—	—	1:8	—	--------	------
	10 Apr. 1944	1.0	24 June 1944	2	—	—	—	1:8	—	--------	------
			25 June 1944	3	—	—	—	1:8	—	--------	------
			26 June 1944	4	—	—	—	1:8	—	--------	------
			30 June 1944	8	1:20	—	-------	1:128	1:8	--------	------
			2 July 1944	10	1:80	—	-------	1:128	1:32	--------	------
			4 July 1944	12	1:160	1:40	-------	1:256	1:32	--------	------
			6 July 1944	14	1:640	—	-------	1:256	1:64	--------	------
			11 July 1944	19	1:1,280	—	-------	1:512	1:64	--------	------
			23 July 1944	31	1:640	1:40	-------	1:512	1:64	--------	------
			29 Aug. 1944	68	1:160	—	-------	1:128	1:32	--------	------
			24 Oct. 1944	124	1:80	—	-------	1:128	1:16	--------	------
			7 Feb. 1946	595	—	—	-------	1:20	—	—	—
3	17 Feb.-28 July 1944.	4.0	6 June 1945	−169	—	—	—	1:10	—	1:40	—
	9 May 1945	1.0	4 Aug. 1945	−110	—	—	—	1:10	—	1:40	—
	1 Oct. 1945	1.0	28 Nov. 1945	7	1:40	—	-------	1:40	—	1:40	—
			5 Dec. 1945	14	1:80	—	-------	1:640	1:160	1:640	1:80
			12 Dec. 1945	21	1:80	—	-------	1:1,280	1:160	1:320	1:80
			26 Dec. 1945	35	1:80	1:80	-------	1:640	1:160	1:320	1:80
			16 Jan. 1946	56	1:40	—	-------	1:320	1:80	1:160	1:40
			6 Feb. 1946	77	—	—	-------	1:320	1:40	1:160	—
			27 Feb. 1946	98	—	—	-------	1:320	1:40	1:160	—
			26 Mar. 1946	125	—	—	-------	1:160	1:20	1:80	—
			9 Nov. 1946	353	—	—	-------	1:40	—	1:80	1:40

[1] Cox-type ether-extracted epidemic typhus vaccine.

[2] Five cubic centimeters of this vaccine was of an experimental bivalent type containing epidemic and murine rickettsiae.

Source: Modified from Sadusk, J. F., Jr.: Typhus Fever in the United States Army Following Immunization; Incidence, Severity of the Disease, Modification of the Clinical Course, and Serologic Diagnosis. J.A.M.A. 133: 1192-1199, 19 Apr. 1947.

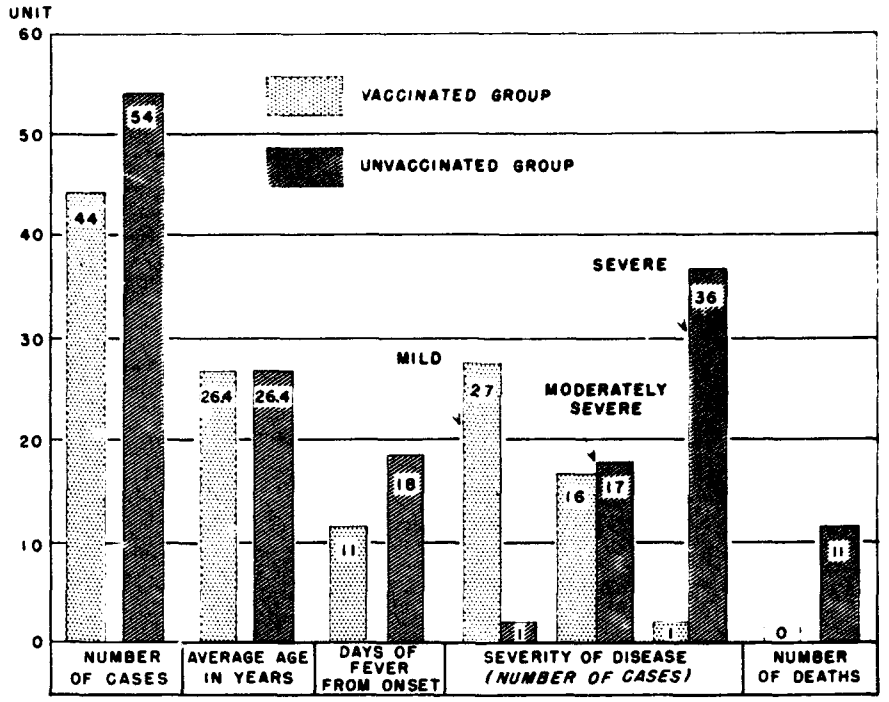
TABLE 16.—*Clinical summary of five cases of epidemic typhus fever incurred subsequent to immunization with typhus fever vaccine*

Case	Age	Sex	Typhus vaccine				Probable manner of infection	Incubation period	Where treated	Severity of illness	Days of fever from onset	Days in bed	Rash	Headache	Confusion	Delirium	WBC
			Total	Date of first dose	Date of last dose	Date of onset of disease											
1	41	M	22.0 cc.	21 Feb. 1942	1 Mar. 1944	21 May 1944	Laboratory, pulmonary inhalation.	Less than 17 days.	Quarters	Mild	6	3	+	+ +	−	−	
2	35	M	14.0 cc.	23 Dec. 1941	10 Apr. 1944	23 June 1944	Laboratory, pulmonary inhalation.	About 12 days.	Hospital	Moderately severe.	10	10	+ +	+ + +	±	−	6,300; 5,600.
3	36	M	6.0 cc.	17 Feb. 1944	1 Oct. 1945	22 Nov. 1945	Field, pulmonary inhalation.	13 days	Quarters	Mild	9	5	−	+ + +	−	−	5,000; 6,600.
4	32	M	3.0 cc.	25 Apr. 1944	9 May 1944	2 Apr. 1945	Field, pulmonary inhalation.	10 days	Hospital	Moderately severe.	11	11	+ + +	+ + +	−	−	7,000; 8,000.
5	45	M	9.5 cc.	August 1944	22 Mar. 1945	2 Apr. 1945	Field, pulmonary inhalation.	10 days	Quarters	Mild	12	5	−	+ + +	−	−	

Source: Modified from Sadusk, J. F., Jr.: Typhus Fever in the United States Army Following Immunization; Incidence, Severity of the Disease, Modification of the Clinical Course, and Serologic Diagnosis. J.A.M.A. 133: 1192-1199, 19 Apr. 1947.

Sadusk's report was in keeping with other observations that the clinical course of epidemic typhus is greatly modified when infection occurs subsequently to vaccination (chart 7). Fever is much lower and of shorter duration than in nonvaccinated cases, the extent and duration of rash are diminished, circulatory and nervous symptoms are lessened, and the incidence of complications is minimal. If hospitalization is necessary, the length of it is reduced. The only symptom that is regularly present in vaccinated cases is severe headache.

CHART 7.—*Clinical comparison of vaccinated and unvaccinated groups of typhus fever cases among employees of the Cairo Fever Hospital, El Abbasa, Egypt*



Source: Ecke, R. S., Gilliam, A. G., Snyder, J. C., Yeomans, A., Zarafonetis, C. J. D., and Murray, E. S.: The Effect of Cox-Type Vaccine on Louse-Borne Typhus Fever in Patients Who Had Previously Received One or More Injections of Cox-Type Vaccine. Am. J. Trop. Med. 25: 447-462, November 1945.

Following is the only case known to have occurred in our troops in Sicily.[25] The patient, a private with the 77th Field Artillery, was admitted to the 59th Evacuation Hospital, Palermo, Sicily, in the summer of 1943. His history and clinical course were recorded by Lt. Col. (later Col.) William A. Reilly, MC, Chief of Medical Service, as follows:

A private claimed he was immunized against typhus in June 1941, and a recall dose was given in June 1943. No record was obtainable. He left Africa on 13 July, after a

[25] (1) Dr. Stanhope Bayne-Jones kindly brought this case report to the attention of the author and made the records available for inclusion here. (2) Letter, Lt. Col. William A. Reilly, MC, Chief of Medical Service, 59th Evacuation Hospital, to Commanding Officer, 59th Evacuation Hospital, North African Theater of Operations, U.S. Army, 21 Sept. 1943, subject: Resume of Typhus Patient's History, Photo, and Chart.

long stay, and arrived in Sicily on 14 July 1943. He does not know of having been bitten by ticks, lice, or fleas.

He was taken ill on 23 August with headache, injected eyes, and fever. Fever disappeared by lysis on 2 September (chart 8). On the third day of disease, 26 August, a maculopapular rash appeared on the trunk, thighs, and arms, gradually increasing in amount, intensity and distribution for the next 5 days and being heaviest on the limbs (*fig.* 11). In spots it was petechial and hemorrhagic and did not fade on pressure. No tache noir or regional lymphadenitis was detected. There was a macular rash on buccal mucosa. The pharynx was slightly reddened. Between the fourth and eighth day, the enlarged spleen was palpable. On the third and seventh day, he had 5,100 and 7,500 WBC normally differentiated and urine specimens were negative except for low specific gravity. The boy was very ill, lost weight and strength. There were a few loose bowel movements between the seventh and ninth days. A blood culture on the fifth day was negative. Weil-Felix tests with the three *Proteus* types were entirely negative on the ninth day in an Italian laboratory. On the 11th day, the *Proteus* OX-19 was positive 1:40, *Proteus* OX-2 was positive 1:160, and *Proteus* OX-K was negative. A third Weil-Felix test, on the 18th day of disease (10 September) showed a rising titer: OX-19 was positive 1:640, OX-2 was positive 1:1,280, and OX-K was negative. A guinea pig inoculated on the 11th day, when temperature was normal for the first time, did not develop scrotal reaction. After fever subsided, the patient gradually recovered strength, weight, and appetite. No complications or sequelae were present 1 month after onset.

Only three confirmed cases of typhus occurred among U.S. troops serving in the European theater, despite its prevalence among the civilian populations.[26] Two infections were contracted in the Rhineland and one in the Inner Reich. All three patients had mild attacks of the disease, as indicated by the following brief case summaries:[27]

Case 4.—A captain of the Medical Corps investigated a typhus outbreak at Fischbach, Germany, on 23 March 1945. He was intimately exposed to the disease while examining and disinfecting patients but does not recall ever having found lice on his person. On 9 April, he developed a macular rash. He was never delirious, stuporous, or disoriented. His convalescence was rapid and uneventful. A Weil-Felix test on 17 April was positive in a serum dilution of 1:640. The patient had not received a stimulating dose of typhus vaccine since the original course in April 1944.

Case 5.—A lieutenant colonel, Medical Corps, accompanied the officer noted in case 4 (above) and both became ill on the same day. This patient's illness was even less severe, with no rash at any time. He remained on quarters status, and returned to duty 15 April. A stimulating dose of typhus vaccine had been administered on 23 March 1945, the day previous to his exposure to the disease. The stimulation antedating that was in September 1944.

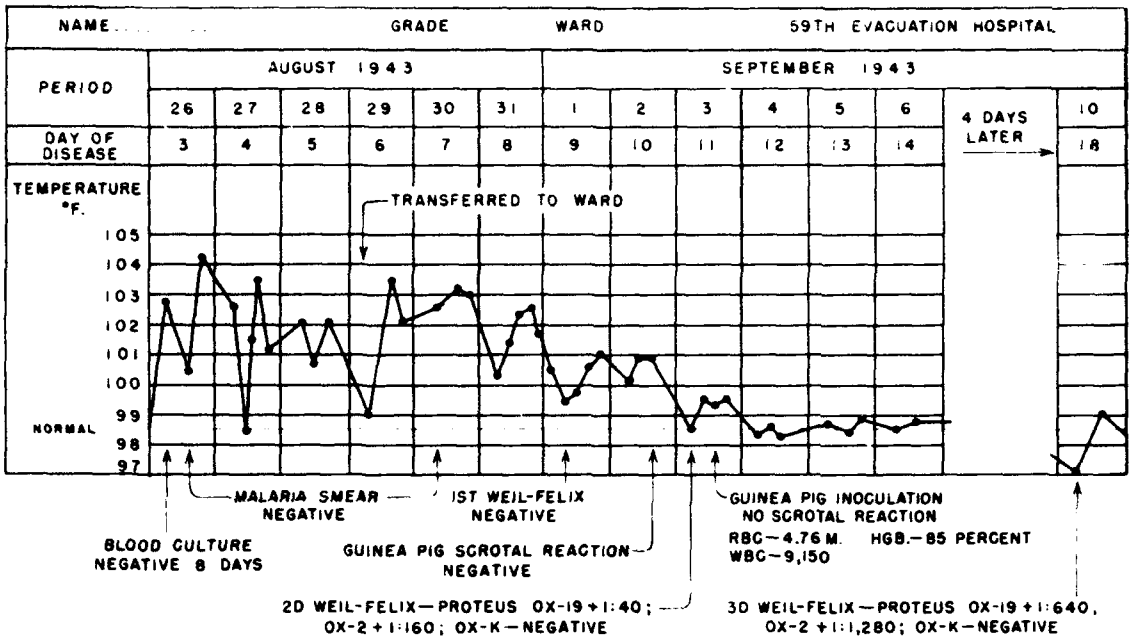
Case 6.—A sergeant of the 15th Infantry became ill 4 April 1945 complaining of pains in the legs, headache, and fever of 102° F. He was admitted to hospital and observed for several days. On 22 April he was transferred to a general hospital with the diagnosis still undetermined. The patient had daily chills with fever up to 104° F. for 11 days and at one time developed a slight rash on the wrists, ankles, and abdomen. A Weil-Felix test performed 5 May was positive in dilution of 1:320. No likely source of infection could be determined and there was clinical difference of opinion as to the identity of the disease.

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[26] See footnote 15, p. 155.

[27] Gordon, John E.: A History of Preventive Medicine in the European Theater of Operations, U.S. Army, 1941-45, vol. I, pt. III, p. 48. [Official record.]

CHART 8.—*Temperature chart and pertinent laboratory findings of the only known case of typhus fever occurring among U.S. Army troops in Sicily, 1943*



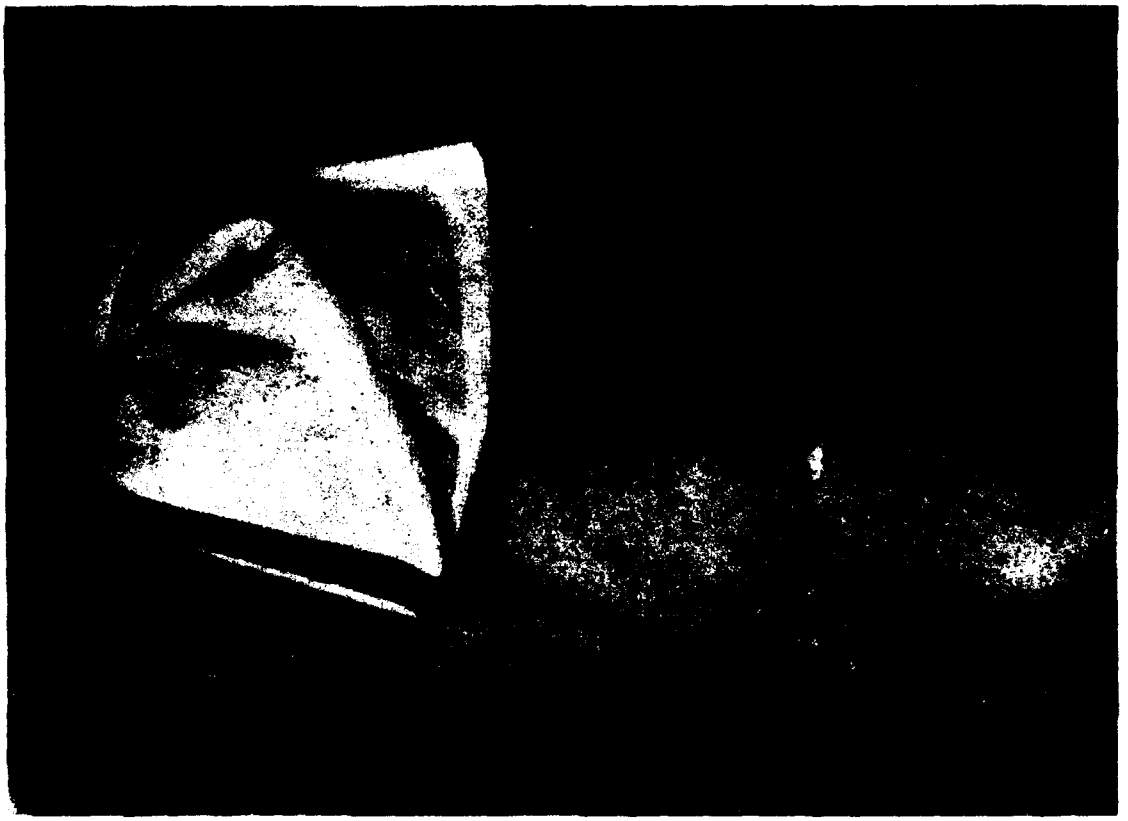


FIGURE 11.—Appearance of maculopapular rash on trunk, thighs, and arms on third day of disease.

The Craigie (British Army) vaccine.—The cases of typhus fever acquired after vaccination that have thus far been described occurred in soldiers who had received vaccine of the Cox type employed in all U.S. Armed Forces, containing, as has been noted, soluble antigen and killed rickettsial micro-organisms of epidemic typhus (*R. prowazeki*). British troops, on the other hand, were inoculated with the Craigie vaccine, which consisted of two parts of epidemic (*R. prowazeki*) and one part of murine typhus (*Rickettsia mooseri*) antigens. Soluble substances as well as killed micro-organisms were included in the Craigie vaccine. In Germany, observing the typhus epidemic at Belsen, Davis[28] also had an opportunity to estimate the value of this vaccine under epidemic conditions, collecting data on 14 cases of typhus in British personnel who had been vaccinated more than 24 days before the onset of their fever. Their clinical courses were milder and shorter than is seen in typical epidemic typhus in nonvaccinated persons, with no deaths and no serious complications. He noted as significant "the absence of serious complications * * *. Parotitis, gangrene, conjunctivitis, deafness due to typhus, epistaxis, pulmonary consolidation, and pleuritic pains were never observed in the British, although all were to be seen in the typhus patients from the concentration camp. Their rash was never extensive, rarely developed into true petechiae which would not blanche on pressure, and never formed ecchymoses. Delirium was observed in only 2 cases, and in these it was brief. Roentgenograms of the chest were reported as normal or 'marked increase in bronchovascular markings throughout both lungs.'" Determinations of blood nonprotein nitrogen were made on 10 patients about a week after the onset of fever. Values ranged from 21 to 42 mg. percent in these cases.

Davis also made observations on 16 cases of typhus in Hungarian soldiers who had only one or two doses of Craigie vaccine after exposure to typhus at Belsen and 41 cases of typhus in well-nourished Germans who had no vaccine. From a comparison of the three groups as shown in table 17, and other data, it was concluded that Craigie vaccine was of definite value in shortening the course and reducing the severity of epidemic typhus fever when given in two or more doses from 24 to 100 days before the onset of the disease.

The course of epidemic typhus fever was thus shown to be modified favorably by prior vaccination with vaccine of either the Cox or the Craigie type. The observations regarding the effectiveness of these two vaccines, however, were not made under controlled or even similar conditions, and it is not possible to draw conclusions as to their relative effectiveness from these data.

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[28] Davis, W. A.: Typhus at Belsen. II. Clinical Course of Epidemic Typhus in Persons Who Had Received Craigie Typhus Vaccine. Ann. Int. Med. 34: 448-465, February 1951.

TABLE 17.—*Comparison of typhus in three groups at Belsen Concentration Camp, Belsen, Germany*

Number	Nationality	Vaccination history	Age (years)	Average age (years)	Duration of fever (days)	Average duration of fever (days)	Deaths (number)
14	British	Two to five doses Craigie vaccine, all given more than 24 days before illness.	20–56	31. 8	6–13	8. 7	0
16	Hungarians	One to two doses Craigie vaccine, none given more than 16 days before illness.	18–38	28. 8	9–15	13. 6	0
41	Germans	No vaccine	20–52	25. 9	13–24	14. 9	2

Source: Modified from Davis, W. A.: Typhus at Belsen. II. Clinical Course of Epidemic Typhus in Persons Who Had Received Craigie Typhus Vaccine. Ann. Int. Med. 34: 448–465, February 1951.

PATHOLOGY

Two important studies of the pathology of epidemic typhus fever were undertaken during World War II. The first of these,[29] by Maj. Arthur C. Allen, MC, and Dr. Sophie Spitz, at the Army Institute of Pathology (now Armed Forces Institute of Pathology), Washington, D.C., entailed a comparison of the histological preparations and protocols of 78 cases of scrub typhus (tsutsugamushi disease), 24 cases of epidemic (louseborne) typhus, 12 cases of Rocky Mountain spotted fever, and lung sections of 2 cases of American Q fever. Since the principal emphasis of this study was placed on the changes induced by scrub typhus, the main findings of the authors are given in the chapter dealing with that infection (p. 132). However, a number of other observations were made which are relevant here. The histology of the cutaneous lesion is described, as follows:

The macule of epidemic typhus histologically was essentially similar to that of scrub typhus, although several differences were found. In the first place, although capillary thrombi were present in all of the available sections of macules of scrub typhus as against only 15, or 65 percent, of the macules in epidemic typhus, the thrombi were considerably more conspicuous in the latter disease. They were more prominent not only because more thrombi occurred in a single section, but because they were larger and were associated with more pronounced endothelial changes. In epidemic typhus, the affected endothelial cells tended to be larger, more hyperchromatic, and more often disintegrated into chromatin dust, the last being a feature observed also in the capillaries of other organs, including the glomerular capillaries. Secondly, there was a tendency to the occurrence in epidemic typhus of a necrotizing arteritis and thrombo-arteritis, not found in scrub typhus. The necrosis might extend through the entire wall of the artery, unlike the lesser degree of involvement that is stated to occur in the experimental animal infected with

[29] Allen, A. C., and Spitz, S.: A Comparative Study of the Pathology of Scrub Typhus (Tsutsugamushi Disease) and Other Rickettsial Diseases. Am. J. Path. 21: 603–681, July 1945.

the rickettsiae of epidemic typhus. Indeed, in the human skin of cases of epidemic typhus there may be infarct like hemorrhagic suppurative necrosis of the portions of corium in association with severe arteritis. Thirdly, whereas no significant changes were noted in the epidermis of the macule of scrub typhus, minor changes consisting of focal spongiosis, patchy parakeratosis and focal "liquefaction degeneration" of the basal layers were infrequently observed in the skin of patients with louse-borne typhus.

The interstitial myocarditis and interstitial pneumonitis of epidemic typhus were intermediate in intensity between that produced by scrub typhus and by spotted fever.

Changes in the adrenal glands of patients with epidemic typhus were similar to those of scrub typhus, except that there was a more conspicuous focal mononuclear reaction. In addition, a few cases of epidemic typhus exhibited inflammatory and degenerative changes of capillaries and arterioles of both parenchymal and adventitial tissues.

Similarly, lesions in the kidneys from patients with epidemic typhus qualitatively resembled those of scrub typhus but were considerably more pronounced. "Acute diffuse glomerulonephritis was found in 18, or 78 percent, of the cases; acute focal glomerulitis in 3, or 13 percent, and essentially normal glomeruli in 2, or 9 percent. The glomerular alterations were basically those of scrub typhus, differing in more marked swelling and hyperchromasia of the endothelial cells, more frequent occurrence of thrombosis of the glomerular capillaries and fragmentation of the endothelial cells. Similarly, focal interstitial infiltrations, calcific bodies, hemoglobin casts of the distal convolutions, and phlebitis, arteritis, and arteriolitis were more conspicuous in epidemic typhus."

A comparison was made between reactions in the brain and meninges in epidemic and scrub typhus. It was found that—

1. Although the meningitis of scrub typhus is slightly more frequent and extensive than the qualitatively similar reaction in epidemic typhus, the involvement of the substance of the brain is considerably greater in the latter disease.

2. The distribution of lesions in the gray and white matter in the two diseases is the same: in both the white matter is spared, in contrast with Rocky Mountain spotted fever.

3. In the current series the case incidence of involvement of the cortex in epidemic typhus is much greater than in scrub typhus. The actual concentration of nodules in the pons, medulla, and basal ganglia in epidemic typhus is more pronounced than in the cortex. The pons and medulla are sites of predilection also in scrub typhus.

Several distinct histologic differences between scrub typhus and epidemic typhus are noted:

4. The nodules tend to be larger in epidemic typhus, averaging 55 to 75 cells as against 15 to 40 cells, and about 120 to 180 μ as against 60 to 120 μ.

5. There is somewhat greater cellular pleomorphism in the nodules of epidemic typhus, especially in the larger. Karyorrhexis is common in the cells of the nodule of epidemic typhus and rare in that of scrub typhus.

6. In epidemic typhus, the capillaries of the nodules show much more obvious evidence of damage in the form of markedly enlarged endothelial cells, karyorrhexis of endothelial cells, and thrombosis of capillaries. Similar changes are found in arterioles without associated nodules.

The character of the tissue reaction in these cases, such as fibrinoid degeneration of collagen, necrosis of lymph nodes and spleen, the predominance of plasma cells and basophilic macrophages, and the acute glomerulonephritis, led these observers to postulate that rickettsiae may exert hyperergic effects in addition to the better known diffuse vascular phenomena caused by them.

The second important investigation of the pathology of epidemic typhus was initiated by the collection of material from 23 fatal cases studied by the U.S.A. Typhus Commission in Cairo, Egypt, during 1943–45, which was reviewed by Spitz and Allen. This, along with material from additional cases, was subsequently studied by members of the Committee on Pathology, Division of Medical Sciences, National Research Council, in collaboration with the Armed Forces Institute of Pathology. The splendid report[30] of this group was not issued until 1953 but because of its broad scope and pertinence to other work discussed in this chapter, the summary statement of this study is quoted, as follows:

> This paper describes the lesions encountered in an epidemic of typhus which occurred in Cairo during 1943–1945. The findings have been compared to those observed by Wolbach, Todd, and Palfrey in the Warsaw epidemic of 1918 and by others since that time in order to bring together in one report all the known facts about the pathology of epidemic typhus.
>
> The patients studied in the Cairo epidemic were Egyptians between the ages of 10 and 70 years. Some of them were undernourished, but there was no clinical or pathological evidence of avitaminosis, and some had clinically inactive schistosomiasis. The patients were admitted to the hospital during the first 2 weeks of their disease, and the clinical diagnosis of louse-borne typhus was confirmed in many cases by the Weil-Felix and complement fixation tests. In some instances rickettsiae were recovered from blood or from normal lice fed on the patients, and each strain isolated showed the characteristics of louse-borne typhus. Two patients were given para-aminobenzoic acid, without clinical or pathological effects. The other patients received no specific antityphus treatment, and none had been vaccinated against typhus. In 14 patients special efforts were made to reduce secondary bacterial infection by using sulfonamides and penicillin when necessary. This paper and the reports of the United States of America Typhus Commission on the clinical and laboratory features constitute one of the few comprehensive accounts of an epidemic of typhus in Egypt or, indeed, in any tropical country. It seems likely, in view of the discovery of antibiotics that may be effective in the treatment of the disease and of the development of satisfactory vaccines, that there may never again be a similar opportunity to study an epidemic of typhus which has not been significantly modified either by treatment or by complicating infection.
>
> The lesions discovered in the Cairo patients were essentially the same as those described in other epidemics in different parts of the world and in experimental animals. The wide dissemination of vascular and other lesions in the skeletal muscles, which was well illustrated by the frequent involvement of the muscles of the tongue, was more apparent in Cairo cases than in others, probably because abundant material was available for microscopic examination. Evidence was obtained by the demonstration of rickettsia-

[30] Pathology of Epidemic Typhus; Report of Fatal Cases Studied by the United States of America Typhus Commission in Cairo, Egypt, During 1943–1945. Prepared by the Committee on Pathology, Division of Medical Sciences, National Research Council With Collaboration of the Armed Forces Institute of Pathology. Arch. Path. 56: 397–435, October; 512–553, November 1953.

like bodies in sections of [illegible]ngs, which suggests, but does not prove, that a true rickettsial pneumonia may [illegible] Interstitial orchitis and prostatitis of a type not ordinarily seen in other infec[illegible]-eases was also observed.

New information has been obtained concerning the topography of lesions in the central nervous system and the effect of the duration of the illness on the intensity of the reaction. So-called microinfarcts have been demonstrated for the first time in the brains of patients who died from epidemic typhus.

Glomerulonephritis did not occur in the Cairo patients, and a review of published articles has led to the conclusion that its occurrence has not been proved. The bulk of the evidence supports the idea that renal failure in epidemic typhus is probably due to extrarenal factors, such as increased protein catabolism, dehydration, and reduction of arterial blood pressure, rather than to primary renal damage brought about by direct action of the rickettsiae. We have not been able to convince ourselves that lower nephron nephrosis occurs.

The pathological observations that have been briefly described here are well illustrated in the Committee's report; selected prints are reproduced as figures 12 through 32, through the courtesy of the *Archives of Pathology*.

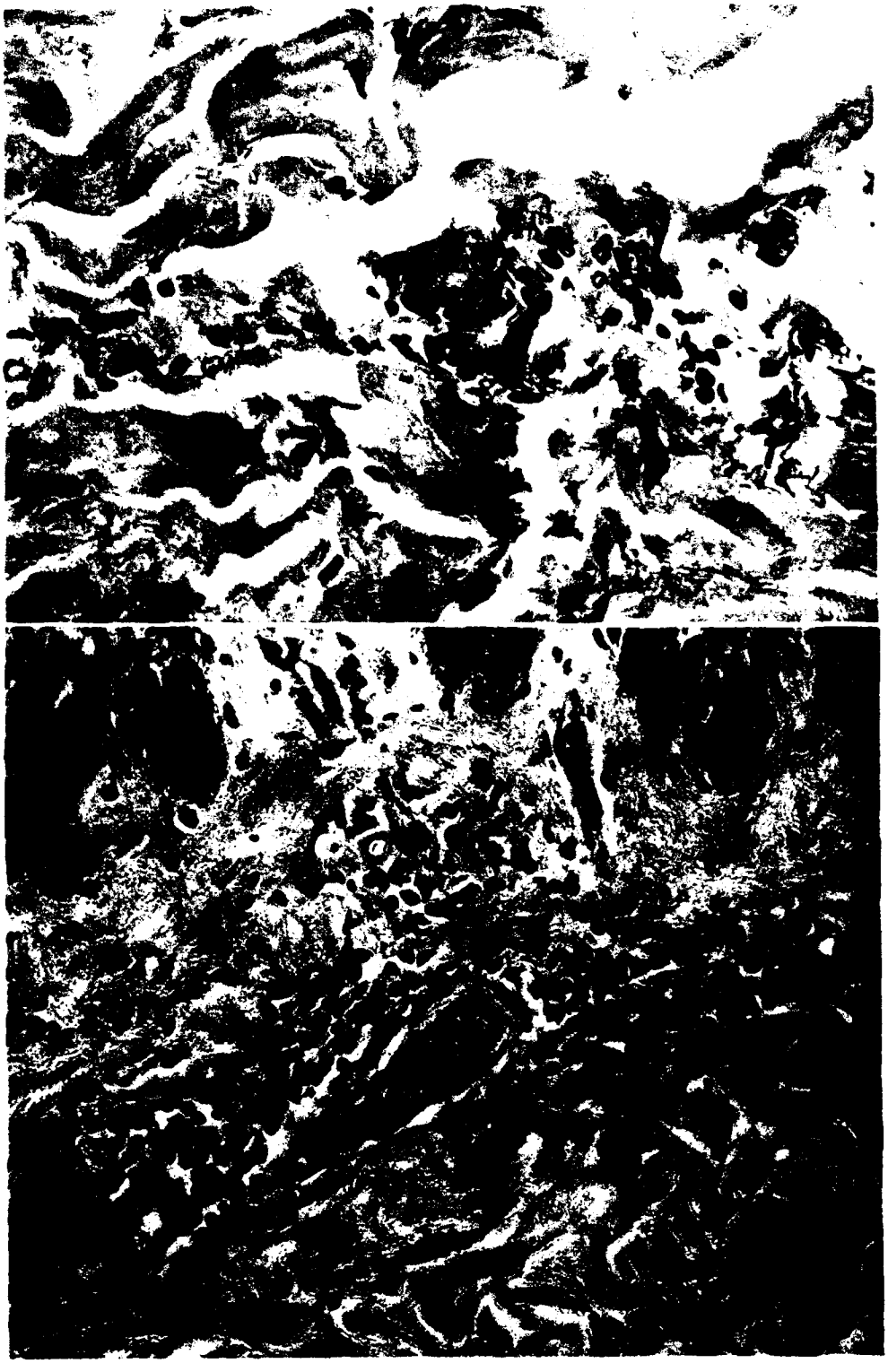


FIGURE 12.—(Top) Capillary in derma showing swelling and proliferation of endothelium to point of occlusion. Slight perivascular accumulation of mononuclear cells. (× 430)

FIGURE 13.—(Bottom) Finely granular capillary thrombus, with pericapillary collection of mononuclear cells in derma. (× 312)

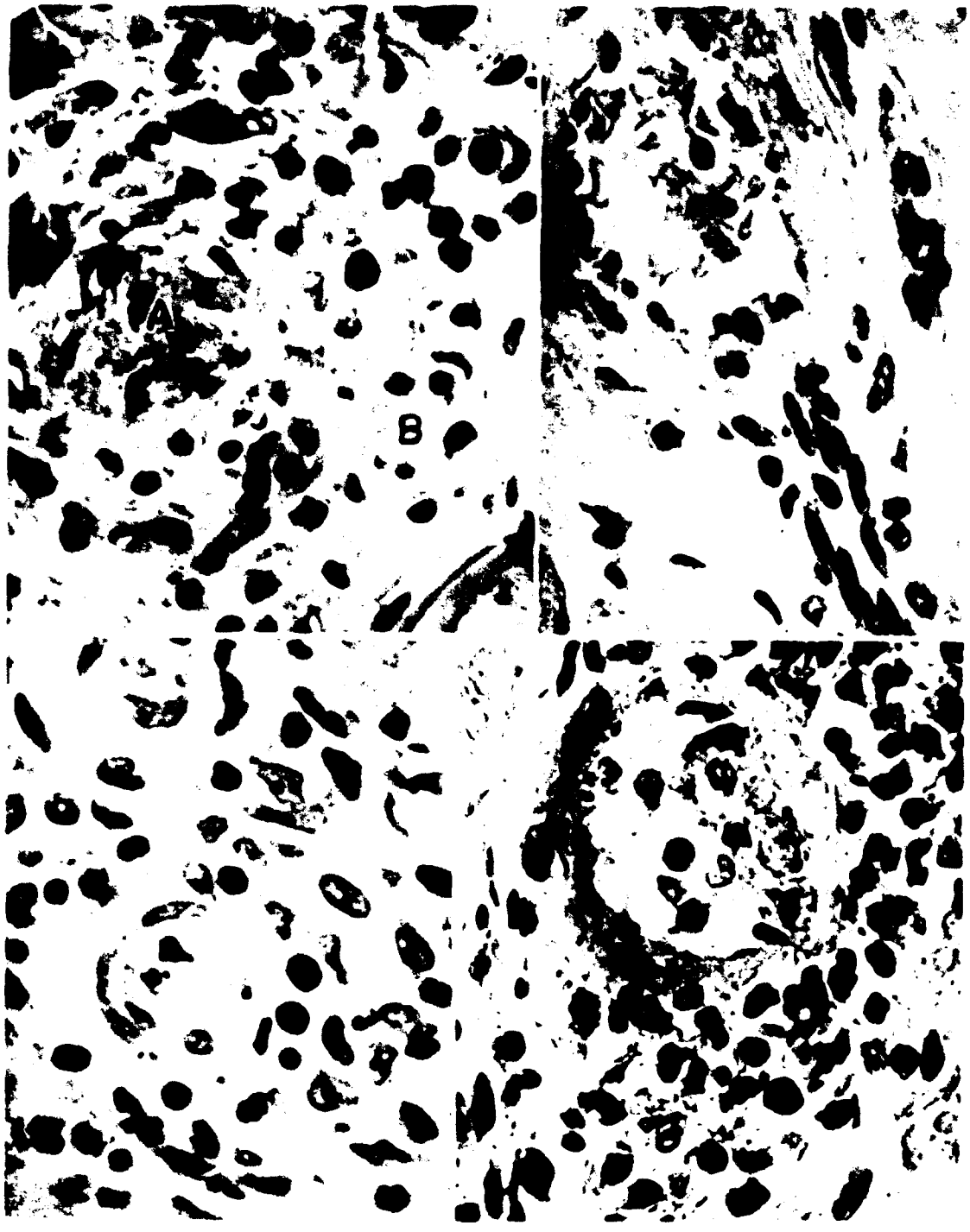


FIGURE 14. (Upper left) Necrosis and thrombosis of dermal capillary (A), with many perivascular mononuclear cells of different types. A small nerve (B) is included. (× 730)

FIGURE 15. (Upper right) Swelling and proliferation of endothelium of capillary in tongue. (× 730)

FIGURE 16. (Lower left) Same case as shown in figure 15. Occlusion of capillary in tongue by swelling and necrosis of endothelium. Pronounced exudation of mononuclear cells in the surrounding tissues. (× 875)

FIGURE 17. (Lower right) Myocardium. Focal swelling and necrosis of capillary endothelium and perivascular infiltration of mononuclear cells with hyperchromatic nuclei. (× 875)

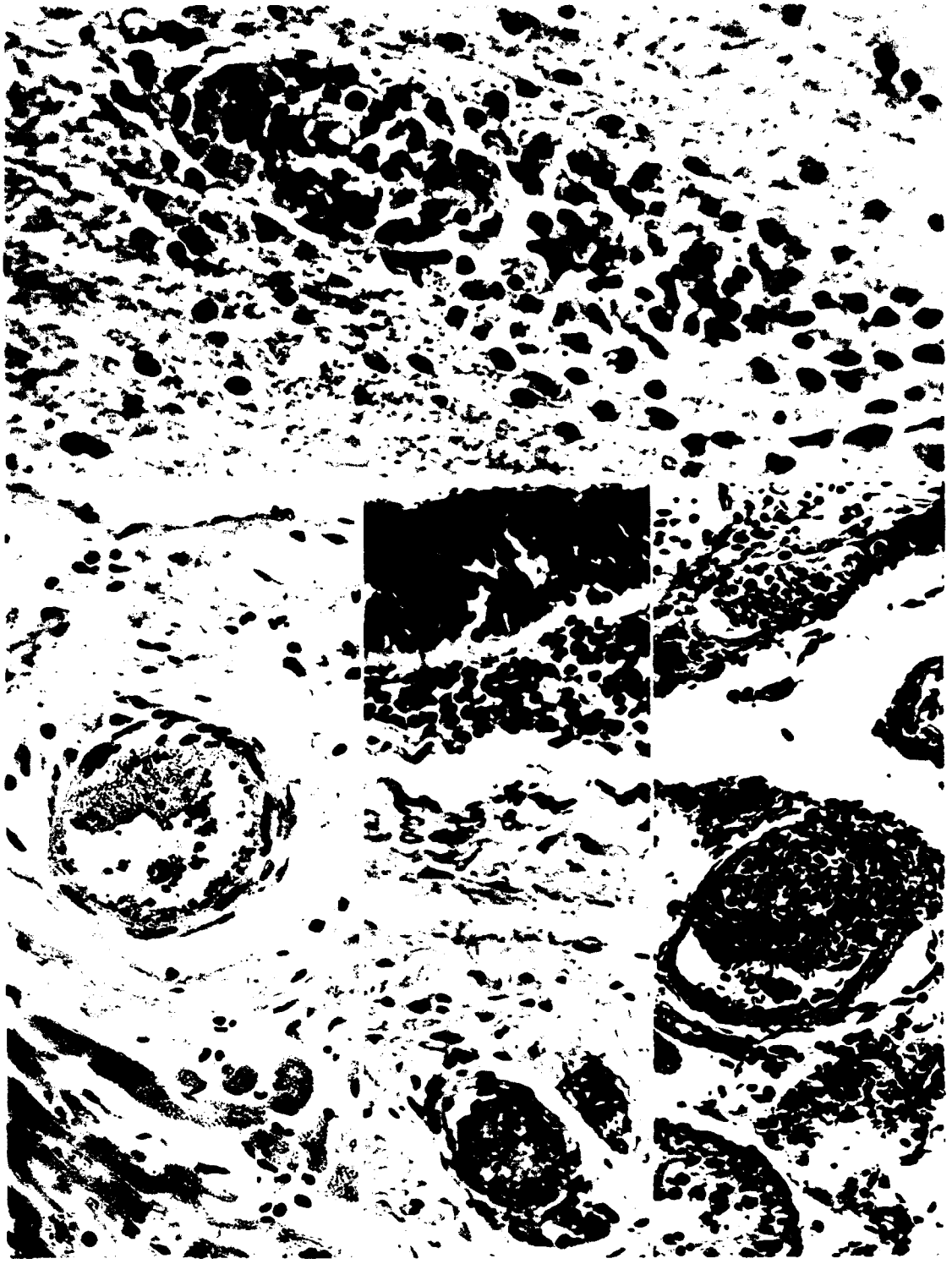


FIGURE 18.—(Top) A large cerebral nodule showing its relation to a capillary in the most compact part. (× 600)

FIGURE 19.—(Lower left) Mural thrombus in subendocardial arteriole, without perivascular infiltration. (× 350)

FIGURE 20.—(Center) Same case as shown in figure 19. Granular thrombus in arteriole in *submucosa* of trachea and cellular infiltrate beneath basement membrane of mucosa. (× 290)

FIGURE 21.—(Right) Cellular thrombus in arteriole of testis. (× 195)



FIGURE 22. (Upper left) Point of attachment of base of mitral valve, with disruption of elastica, edema (mucoid), infiltration of mononuclear cells, and production of fibroblasts. (× 312)

FIGURE 23. (Upper right) Acute interstitial myocarditis, with diffuse infiltration of mononuclear cells. (× 312)

FIGURE 24. (Lower left) Same case as shown in figures 19 and 20. Acute interstitial myositis of tongue, with infiltration of mononuclear cells. (× 155)

FIGURE 25. (Lower right) Small nodule of mononuclear cells in skeletal muscle attached to thyroid gland. (× 310)

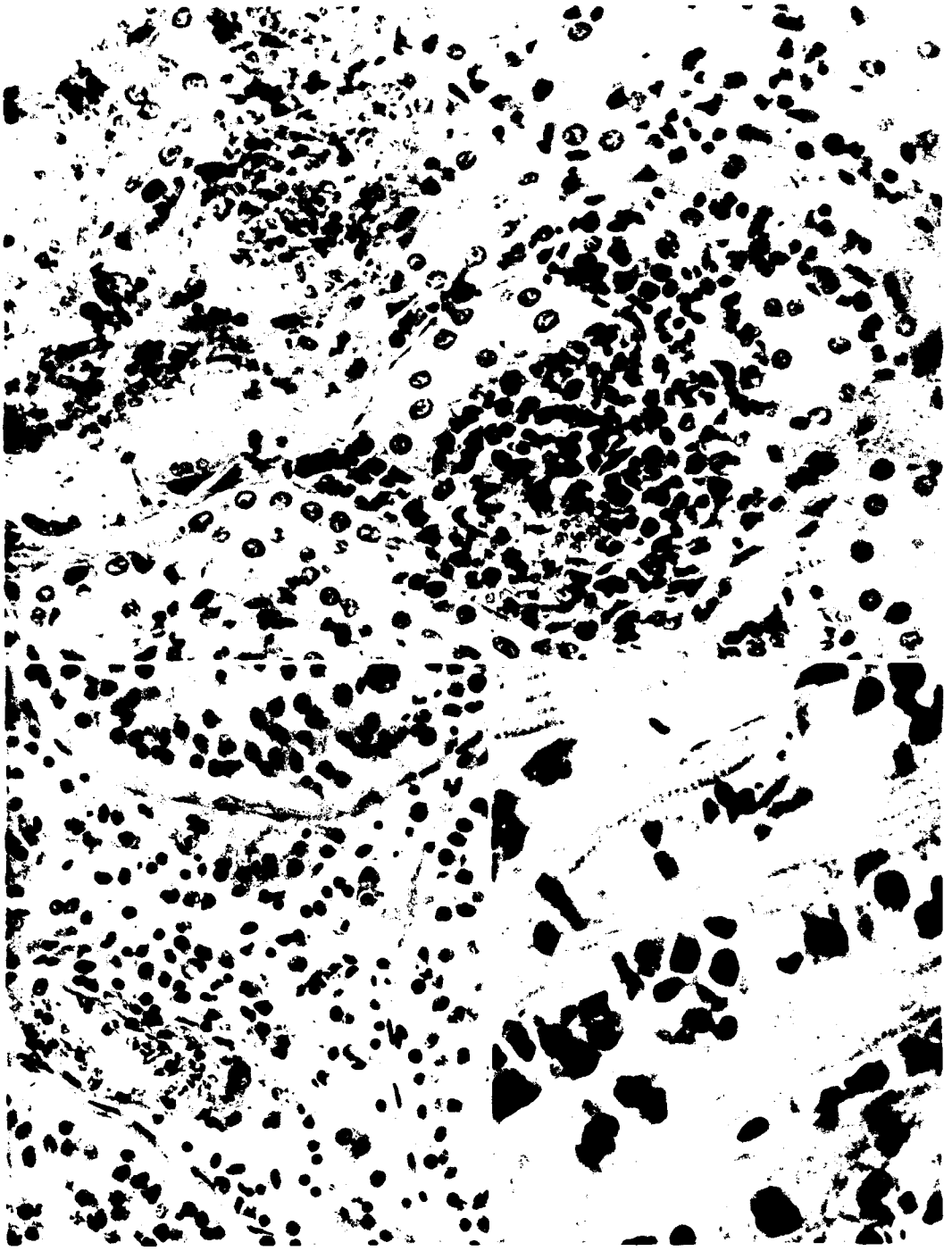


FIGURE 26.—(Top) Mononuclear infiltrate in corticomedullary *junction of kidney*. Numerous cells have abundant basophilic cytoplasm and an eccentrically placed nucleus similar in chromatin pattern to that of plasma cells. Some of these are within the lumen of the small vessel, and the remainder are interstitial between the renal tubules. Numerous red blood cells are visible in the neighboring loops of Henle. The patient was a 30-year-old male, the duration of whose illness was not known. (× 400)

FIGURE 27. (Lower left) Focal interstitial orchitis about a dilated capillary. The exudate is composed of large mononuclear cells, plasma cells, and lymphocytes. (× 300)

FIGURE 28. (Lower right) Mononuclear cells forming interstitial exudate in acute myocarditis. Myocardial fibers are preserved. (× 875)

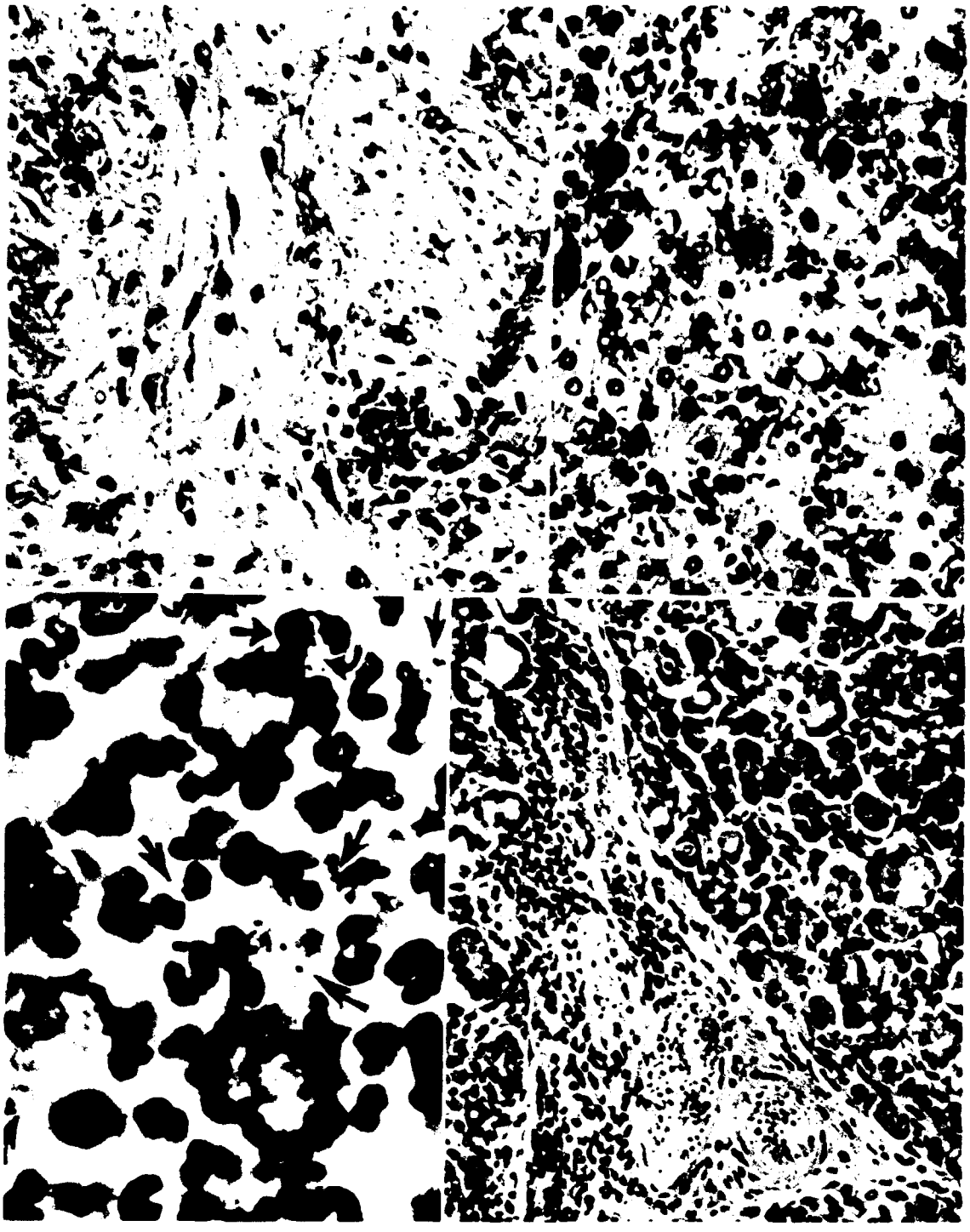


FIGURE 29. (Upper left) Same case as shown in figure 23. Nodules in posterior lobe of pituitary identical with those in the brain and spinal cord. (× 250)

FIGURE 30. (Upper right) Same case as shown in figure 21. Hyperplasia of sinusoidal endothelium of the liver and infiltration of mononuclear cells. (× 250)

FIGURE 31. (Lower left) Lung, alveolar exudate showing many rickettsia-like bodies in cytoplasm of polymorphonuclear leukocytes. Nyka stain. (× 1,450)

FIGURE 32. (Lower right) Pancreas, infiltration of mononuclear cells in the interlobular septum, dilatation of acini, and inspissation of secretion. (× 205)

DEVELOPMENT AND USE OF LABORATORY AIDS IN DIAGNOSIS

Along with the advances in louse-control measures and immunization, and extension of fundamental knowledge of the clinical and pathological aspects of the disease, progress was also made during World War II in the development of diagnostic laboratory procedures for epidemic typhus fever. The most active work in this connection was performed at the Division of Virus and Rickettsial Diseases, Medical Department Professional Service Schools, Army Medical Center, Washington, D.C., at the Cairo Unit of the U.S.A. Typhus Commission, and at the National Institutes of Health in Bethesda, Md.

Weil-Felix test.—In 1916, Felix [31] demonstrated that sera from patients with epidemic typhus fever would agglutinate suspensions of *Proteus* microorganisms. Although it was soon recognized that these bacteria were not etiologically related to typhus fever, the agglutination of *Proteus* organisms was quickly developed into a diagnostic test for typhus. Further study revealed that *Proteus vulgaris* organisms could be dissociated into a motile flagellated "H" type and a nonmotile unflagellated "O" type. The diagnostic agglutinin that appears in the blood of typhus fever patients is the somatic "O" type. Additional experience prior to World War II indicated that suspensions of the *Proteus* OX–19 strain were agglutinated by sera from typhus fever cases; that OX–19 and another strain, *Proteus* OX–2, were often agglutinated by Rocky Mountain spotted fever sera; and that suspensions of still another variant, *Proteus* OX–K, were agglutinated by scrub typhus sera (p. 133). There remained, however, conflicting statements as to the time of appearance of the agglutinins during the course of illness, and concerning what constituted a significant or diagnostic titer. Accordingly, early in 1943, Plotz sought to determine the rise and fall of the various types of demonstrable antibodies in cases of epidemic typhus fever. Serial serum specimens were obtained from 32 untreated and unvaccinated typhus fever cases studied by members of the Typhus Commission in Cairo. Blood specimens were obtained early in the disease, during the course of illness, and as long after convalescence as possible. It was thus possible to establish patterns of antibody dynamics in cases confirmed, in 21 instances, as epidemic typhus by isolation of the strain. The results of the various serological tests performed on these sera were summarized in an important series of papers from the Army Medical School.[32]

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[31] Felix, A .: Die Serodiagnostik des Fleckfiebers. Wien. klin. Wchnschr. 29: 873-877, 13 July 1916.

[32] (1) Plotz, H., Wertman, K., and Bennett, B. L.: The Serological Pattern in Epidemic Typhus Fever. I. The Development of Complement Fixing Antibodies. Division of Virus and Rickettsial Diseases, Army Medical School, Army Medical Center, Washington, D.C., 1944. [Official record.] (2) Plotz, H., Wertman, K., and Bennett, B. L.: The Serological Pattern in Epidemic Typhus Fever. II. The Weil-Felix Reaction. Division of Virus and Rickettsial Diseases, Army Medical School, Army Medical Center, Washington, D.C., 1944. [Official record.] (3) Plotz, H., and Bennett, B. L.: The Serological Pattern in Epidemic Typhus Fever. III. The Neutralizing Antibody. Division of Virus and Rickettsial Diseases, Army Medical School, Army Medical Center, Washington, D.C., 1944. [Official record.]

In these cases, there was usually a high *Proteus* OX–19 agglutination titer, a low OX–2, and a negative OX–K reaction. A rise in titer was found in all cases when early and late specimens were compared. A test was regarded as having diagnostic significance when the titer rose fourfold, occurring, in this group of cases, by the 5th to the 13th day of disease. Tests on followup sera showed that the titer had fallen to insignificant levels within about 3 months after the onset of illness. Table 18 shows the characteristic pattern as observed in one of these patients.

TABLE 18.—*Weil-Felix* Proteus *agglutination tests in epidemic typhus (case 1344)- strain isolated*

Day of disease	Serum titer with *Proteus*—		
	OX-19	OX-2	OX-K
4th	0	0	0
5th	0	0	0
6th	0	0	0
8th	1:20	0	0
10th	1:320	1:20	0
12th	1:1,280	1:40	0
14th	1:640	1:40	0
19th	1:640	1:160	0
20th	1:640	1:80	0
23d	1:640	1:80	0
25th	1:320	1:80	0
27th	1:160	1:40	0
115th	1:20	1:20	0
286th	1:20	1:10	0
713th	1:40	0	0

Source: Wertman, Kenneth: The Weil-Felix Reaction. *In* Rickettsial Diseases of Man. Washington: American Association for the Advancement of Science, 1948, pp. 184–189.

Using the identical macroscopic agglutination technique as employed in the Division of Virus and Rickettsial Diseases, Zarafonetis [33] performed Weil-Felix tests on 1,002 sera from 203 cases of epidemic typhus fever. Two or more serum samples were tested from each of the patients who had been studied clinically in Egypt, Greece, Yugoslavia, and the Dachau Concentration Camp in Germany. All of these patients had survived their disease, and sufficient time had elapsed for the development of antibodies if they were to appear in amounts detectable by these tests. A summary of the

(4) Plotz, H., and Snyder, J. M.: The Serological Pattern in Epidemic Typhus Fever. IV. Rickettsial Agglutination. Division of Virus and Rickettsial Diseases, Army Medical School, Army Medical Center, Washington, D.C., 1944. [Official record.]

[33] Zarafonetis, C. J. D.: The Serological Reactions in the Rickettsial Diseases of Man. *In* Rickettsial Diseases of Man. Washington: American Association for the Advancement of Science, 1948, pp. 179–183.

Proteus OX–19 agglutination results is given in table 19. An agglutination titer of 1:160 or more developed in 191 (or 94 percent) of these subjects. Sera in five cases were entirely negative, sera in four others gave complete agglutination only to a dilution of 1:40, and in three more, to 1:80. Of interest was the finding that the complement fixation tests yielded diagnostic titer changes in all of these patients. Thus were the Weil-Felix and complement fixation reactions found to be dissociated phenomena. A similar dissociation was also demonstrated for the Weil-Felix and rickettsial agglutination responses. (See p. 185.) This significant observation is illustrated in table 20.

TABLE 19.—*Weil-Felix* Proteus *OX–19 agglutination results on 1,002 sera from 203 patients with typhus fever*

Maximum titer [1]	Cases	Cases cumulative	Percent	Percent cumulative
Negative	5	203	2.5	100.0
1:40	4	198	2.0	97.5
1:80	3	194	1.5	95.5
1:160	9	191	4.4	94.0
1:320	13	182	6.4	89.6
1:640	21	169	10.3	83.2
1:1,280	24	148	11.8	72.9
1:2,560	30	124	14.8	61.1
1:5,120 and over	94	94	46.3	46.3
Total	203		100.0	

[1] Complete agglutination in dilution given.

Source: Zarafonetis, C. J. D.: The Serological Reactions in the Rickettsial Diseases of Man. *In* Rickettsial Diseases of Man. Washington: American Association for the Advancement of Science, 1948, pp. 179–183.

Wertman [34] summarized the wartime experience with the Weil-Felix reaction and constructed the following table to indicate the usual findings in the various rickettsial diseases of man (table 21). He pointed out that, despite the introduction of specific diagnostic reagents, the Weil-Felix reaction remained a valuable laboratory aid, as follows:

* * * The value of the *Proteus* agglutination test is that these antibodies appear somewhat earlier than the specific ones. The antigen is easy to prepare and the technic can be performed in any diagnostic laboratory. It should be emphasized, however, that a significant test is one in which a rise in antibody titer can be demonstrated and no single titer should be regarded as significant. Since one rickettsial disease cannot be differentiated from another by means of this test, it must be regarded as only a diagnostic aid. The demonstration of the presence of specific antibodies, either complement fixing or rickettsial agglutinating, is necessary to establish a final serologic diagnosis.

[34] Wertman, Kenneth: The Weil-Felix Reaction. *In* Rickettsial Diseases of Man. Washington: American Association for the Advancement of Science, 1948, pp. 184–189.

TABLE 20.—*Serological findings in three typhus cases with negative Weil-Felix OX-19 agglutination results*

Case	Day of disease	Serological findings				
		Weil Felix OX-19	Complement fixation		Rickettsial agglutination	
			Epidemic	Murine	Epidemic	Murine
566	8	Negative	1:640	1:40	1:640	1:320
	15	1:20	1:2,560 [1]	1:320	1:10,240	1:5,120
	22	Negative	1:1,280	1:160	1:5,120	1:2,560
	30	do	1:1,280	1:80	1:2,560	1:1,280
	90	do	1:160	1:10	1:160	1:40
2048	5	do	1:256	Negative	1:1,280	1:320
	10	do	1:1,024	1:8	1:5,120	1:1,280
	15	do	1:512	Negative	1:2,560	1:640
	112	do	1:32	do	1:80	1:80
3696	12	do	1:64	do	1:320	1:160
	17	do	1:1,024	do	1:1,280	1:640
	34	do	1:1,024 [1]	do	1:640	1:640
	43	do	1:1,024	do	1:640	1:320
	47	do	1:512	do	1:640	1:160
	77	do	1:512	do	Negative	Negative
	117	do	1:128	do	do	Do.

[1] End point titer was not reached.

Source: Zarafonetis, C. J. D.: The Serological Reactions in the Rickettsial Diseases of Man. *In* Rickettsial Diseases of Man. Washington: American Association for the Advancement of Science, 1948, pp. 179–183.

TABLE 21.—*The usual Weil-Felix reactions in rickettsial diseases*

Diseases	Proteus		
	OX-19	OX-2	OX-K
Epidemic typhus	+ + + +	+	0
Murine typhus	+ + + +	+	0
Scrub typhus	0	0	+ + + +
Q fever	0	0	0
Rocky Mountain spotted fever	+ + + +	+	0
	+	+ + + +	0

Source: Wertman, Kenneth: The Weil-Felix Reaction. *In* Rickettsial Diseases of Man. Washington: American Association for the Advancement of Science, 1948, pp. 184–189.

Wertman further describes the limitations of the Weil-Felix reaction:

In the first instance, it is impossible to differentiate epidemic typhus, murine typhus, and Rocky Mountain spotted fever by this technic. * * * Secondly, positive reactions have been reported with sera from cases other than those of rickettsial origin. * * * Lastly, the *Proteus* agglutinins in rickettsial infections disappear in late convalescence: therefore, the test cannot be employed as a survey tool to determine the qualitative or quantitative degree of past infection in a given area.

The next step was to determine what serological changes were induced by vaccination as carried out in U.S. troops with vaccine of the Cox type. In a series of serological studies at the Cairo laboratory of the Typhus Commission,[35] it was demonstrated, first, that a 1.0 ml. stimulating dose of typhus vaccine in 100 multivaccinated individuals resulted in no significant change in Weil-Felix agglutination titers in tests with suspensions of *Proteus* OX–19, OX–2, and OX–K on sera taken before and 2 weeks after the injection. Secondly, no anamnestic reactions were detected when these tests were performed on sera from 104 febrile patients who had previously been vaccinated. Finally, serological tests were performed on serial serum specimens from 29 cases of suspected epidemic typhus developing subsequently to vaccination. Here, it was found that the titer changes in *Proteus* OX–19 agglutination tests were greater than those in the first and second groups and were, furthermore, of sufficient magnitude to have diagnostic significance. Examples of results in typhus cases occurring after vaccination are given in table 15.

Complement fixation tests with rickettsial antigens.—Numerous investigators were aware of the limitations of the Weil-Felix tests and strove to develop specific rickettsial antigens for use in complement fixation and agglutination tests. The preparation of pure suspensions of rickettsiae in sufficient quantity was an obstacle until, in 1938, Cox introduced the yolk-sac culture method. Using this method of rickettsial cultivation, Bengtson[36] prepared antigens and successfully performed complement fixation tests upon sera from murine typhus cases. In 1942, Craigie[37] demonstrated that rickettsiae could be separated from yolk-sac suspensions by ether extraction, thereby eliminating most of the embryonic egg materials. This made available essentially pure suspensions of rickettsiae for use as antigens in serological tests and vaccines. Indeed, Wertman[38] later showed that this method actually increased the specificity of the rickettsial suspensions by removing about half of the syphilitic antigens normally present in tissues of the embryonic chick. Plotz and his associates[39] soon noted that sera from both epidemic and murine typhus patients gave complement fixation titers with both epidemic and murine antigens. These investigators found that by repeated washing and centrifugation of the rickettsial suspensions a "soluble substance" present in the supernatant fluid could be removed. This process

[35] (1) Zarafonetis, C. J. D.: Serologic Studies in Typhus-Vaccinated Individuals. I. The Effect of a Stimulating Dose of Typhus Vaccine on the Weil-Felix and Complement-Fixing Antibodies. J. Immunol. 51: 365–374, November 1945. (2) Zarafonetis, C. J. D.: Serologic Studies in Typhus-Vaccinated Individuals. II. The Effect of Non-Typhus Fevers on the Weil-Felix and Complement-Fixing Antibodies. J. Immunol. 51: 375–388, December 1945. (3) Zarafonetis, C. J. D., Ecke, R. S., Yeomans, A., Murray, E. S., and Snyder, J. C.: Serologic Studies in Typhus-Vaccinated Individuals. III. Weil-Felix and Complement-Fixation Findings in Epidemic Typhus Fever Occurring in the Vaccinated. J. Immunol. 53: 15–30, May 1946.

[36] Bengtson, I. A.: Complement Fixation in Endemic Typhus Fever. Pub. Health Rep. 56: 649–653, 28 Mar. 1941.

[37] See footnote 19, p. 156.

[38] Wertman, K.: Nonspecific Complement-Fixing Antigen in Embryonic Egg Tissues. J. Lab. & Clin. Med. 30: 112, February 1945.

[39] See footnotes 32 (1), p. 179; and 20 (1), p. 156.

also served to eliminate the remainder of the syphilitic antigen. The resuspended rickettsial suspensions were then shown to be essentially specific for homologous sera. Thus was made possible the serological differentiation between epidemic and endemic typhus, with obvious epidemiological as well as clinical significance.

This specific complement fixation test was used in several laboratories, but comprehensive data for nonvaccinated cases were recorded primarily at the Army Medical School and by the Cairo Unit of the Typhus Commission. At the Army Medical School, Plotz and his coworkers performed systematic complement fixation tests on the sera from the Cairo series of 32 unvaccinated patients with typhus fever (p. 179). All of these patients showed a rise in titer in tests with epidemic antigen; 56 percent gave positive complement fixation by the 10th day, 78 percent by the 12th day, and 100 percent by the 16th day of illness. Most of them gave fixation with epidemic antigen and no fixation with murine antigen (table 22). Where cross-fixation did occur, the titer with homologous (epidemic) antigen was always higher than with murine antigen. All cases showed persistence of complement fixing antibodies, even when specimens taken many months after onset of the disease were examined.

TABLE 22.—*Complement fixation test results in case 1344, epidemic typhus—strain isolated*

Day of disease	Serum titer with—	
	Epidemic antigen	Murine antigen
4th	0	0
5th	0	0
6th	0	0
8th	0	0
10th	1:20	0
12th	1:1,280	0
14th	1:1,280	0
19th	1:640	0
20th	1:640	0
23d	1:640	0
25th	1:640	0
27th	1:640	0
115th	1:80	0
286th	1:40	0

Source: Plotz, H., Wertman, K., and Bennett, B. L.: The Serological Pattern in Epidemic Typhus Fever. I. The Development of Complement Fixing Antibodies. Division of Virus and Rickettsial Diseases, Army Medical School, Army Medical Center, Washington, D.C., 1944. [Official record.]

Employing the same technique and antigens prepared by the Division of Virus and Rickettsial Diseases, Zarafonetis [40] performed complement fixation tests on 1,002 sera from 203 cases of typhus fever, with results sum-

[40] See footnote 33, p. 180.

marized in table 23. Almost all of the cases were epidemic typhus fever, confirmed in many instances by isolation of the strain. In only two patients did the complement fixation titer with murine antigen equal or exceed that obtained with epidemic antigen. Sera from two of the cases failed to develop titers in complement fixation tests with either epidemic or murine typhus antigens, while both showed good responses in Weil-Felix OX–19 and rickettsial agglutination tests. From the serological findings in these two cases (table 24), it appears that the rickettsial agglutination response is dissociated from the antibody that gives rise to complement fixation. From this and from similar observations with the Weil-Felix test (p. 181), it is seen that all three of the serological reactions occur independently of one another, and one test may be negative while the other two give a positive finding for typhus fever.

TABLE 23.—*Complement fixation results on 1,002 sera from 203 patients with typhus fever*

Maximum titer	Purified epidemic antigen				Purified murine antigen			
	Cases	Cases cumulative	Percent	Percent cumulative	Cases	Cases cumulative	Percent	Percent cumulative
	Number	*Number*			*Number*	*Number*		
Negative	3	203	1.5	100.0	124	203	61.1	100.0
1:8 or 1:10	0	200	0	98.5	11	79	5.4	38.9
1:16 or 1:20	2	200	1.0	98.5	16	68	7.9	33.5
1:40	3	198	1.5	97.5	21	52	10.3	25.6
1:64 or 1:80	18	195	8.9	96.0	12	31	5.9	15.3
1:128 or 1:160	28	177	13.8	87.1	4	19	2.0	9.4
1:256 or 1:320	37	149	18.2	73.3	8	15	3.9	7.4
1:512 or 1:640	46	112	22.6	55.1	5	7	2.5	3.5
1:1,024 or over	66	66	32.5	32.5	2	2	1.0	1.0
Total	203		100.0		203		100.0	

Source: Zarafonetis, C. J. D.: The Serological Reactions in the Rickettsial Diseases of Man. *In* Rickettsial Diseases of Man. Washington: American Association for the Advancement of Science, 1948, pp. 179–183.

It now remained to determine the effect of vaccination per se on the complement fixing antibodies. Tests were made on sera taken before and 2 weeks after a 1.0 ml. stimulating dose of typhus vaccine in 100 multivaccinated subjects (p. 183). Sera from 21 of these individuals gave epidemic complement fixation titers ranging from 1:4 to 1:32 before the stimulating dose, while 2 weeks later sera from 70 of the subjects were positive in dilutions ranging from 1:4 to 1:128. Where there was an increase in complement fixation titer as a result of booster vaccination, there was a tendency to return to the previous level within 8 weeks after the booster injection.

The question of anamnestic reactions was studied in 104 persons who had been immunized with vaccine of the Cox type at some time before the

TABLE 24.—*Serological findings in two cases of typhus fever with negative results in complement fixation tests*

Case	Day of disease	Serological findings				
		Weil-Felix OX-19	Complement fixation		Rickettsial agglutination	
			Epidemic	Murine	Epidemic	Murine
16261	4	1:160	Negative	Negative	—	—
	6	1:1,280	do	do	Negative	1:160
	8	1:5,120 [1]	do	do	1:40	1:1,280
	10	1:5,120 [1]	do	do	1:160	1:2,560
	12	1:5,120 [1]	do	do	1:160	1:10,240
	15	1:5,120 [1]	do	do	1:320	1:5,120
	17	1:5,120 [1]	do	do	1:320	1:5,120
D–857	4	1:160	do	do	1:160	1:40
	11	1:1,280	do	do	1:1,280	1:320
	18	1:1,280	do	do	1:1,280	1:160
	24	1:640	do	do	1:320	1:80

[1] End point titer was not reached.

Source: Zarafonetis, C. J. D.: The Serological Reactions in the Rickettsial Diseases of Man. *In* Rickettsial Diseases of Man. Washington: American Association for the Advancement of Science, 1948, pp. 179–183.

febrile illness that led to their hospitalization (p. 183). No significant increase in complement fixing antibodies occurred in them as a result of the nontyphus fevers.

With these studies as background, Zarafonetis and his coworkers,[41] studying 29 vaccinated patients with probable epidemic typhus fever, found that the diagnosis could be made serologically provided the possible effects of vaccination per se were evaluated as well. A higher degree of cross-fixation was encountered in these tests than had been found in nonvaccinated patients with epidemic or murine typhus fever. An example is shown in table 25. This patient was proved to have epidemic typhus fever by isolation of the strain. The high degree of cross-fixation present in the sera was not due to a peculiarity of the strain itself, since sera from guinea pigs infected with it gave high titers in complement fixation tests with epidemic antigen but were negative in tests with murine antigen. Because of the observed cross-fixation, it was deemed unjustifiable to attempt differentiation between epidemic and murine typhus in vaccinated persons on the basis of the complement fixation test alone.

In seeking an explanation for the cross-fixation, it was noted that the same lots of antigen were used in both the vaccinated and the unvaccinated groups and in the latter revealed no lack of specificity. Again, tests on sera from guinea pigs infected with two strains isolated from the vaccinated patients gave clear-cut identification of epidemic typhus fever. Accordingly,

[41] See footnote 35 (3), p. 183.

TABLE 25.—*Serological findings in a patient with epidemic typhus fever* [1] *contracted after receiving 5.0 cc. of Cox-type vaccine*

Day of disease	Serological findings		
	Weil-Felix OX-19	Complement fixation	
		Epidemic	Murine
8th	Negative	1:4	Negative
19th	1:160	1:512	1:512
30th	1:160	1:512	1:512
40th	1:80	1:512	1:256
83d	Negative	1:512	1:128
162d	do	1:256	1:16

[1] Verified by strain isolation.

Source: Zarafonetis, C. J. D.: The Serological Reactions in the Rickettsial Diseases of Man. *In* Rickettsial Diseases of Man. Washington: American Association for the Advancement of Science, 1948, pp. 179–183.

with the antigens known to be specific and the possibility of "intermediate" strains ruled out, it appeared that the increased amount of cross-fixation was the result of the vaccination itself. Furthermore, in vaccinated subjects without typhus there was a higher amount of cross-fixation than one would expect. It appeared, therefore, that vaccination introduces some factor that gives rise to cross-fixation and that this is simply exaggerated by subsequent infection. The following hypothesis was advanced:

Several workers have noted the presence of a soluble substance in epidemic and murine rickettsial suspensions derived from infected yolk sacs. This soluble substance is common to both strains and if present in antigens used in complement fixation tests is responsible for cross-fixation with heterologous sera. Plotz and his coworkers removed this soluble antigen from rickettsial suspensions and these purified rickettsial antigens gave little or no heterologous fixation. The antigens used in this laboratory are similarly purified rickettsial suspensions and have demonstrated their specificity in nonvaccinated typhus cases.

While this soluble material is responsible for cross-fixation in complement fixation tests, it also has immunogenic properties. Topping and his associates have found that this material produced positive Weil-Felix reactions in rabbits, and that guinea pigs were immunized as judged by the stimulation of immunity to challenge with guinea pig passage material. They also found that it produced complement fixing antibodies when injected into guinea pigs. These findings were considered sufficient to warrant the retention of the soluble material in vaccine preparations such as are in use today.

Thus, antigens for complement fixation tests are purified by removing the soluble substance, while vaccines retain it for its immunogenic properties. Therefore, an individual vaccinated with Cox-type epidemic typhus vaccine receives both epidemic rickettsiae and soluble substance. It seems reasonable to assume that an immunogenic response will be elicited by both of these components of the vaccine, though this may not necessarily be detected in serologic tests. Subsequent infection with typhus rickettsiae stimulates a further antibody response, including a soluble substance component which fixes complement in the presence of both epidemic and murine antigens. In other words, a complement fixing antibody against both epidemic and murine rickettsiae results from inocula-

tion with vaccine containing a soluble substance. This antibody gives rise to cross-fixation, thus tending to counteract the specificity of antigens purified by removing the soluble substance.

Rickettsial agglutination.—Limited agglutination studies with rickettsial suspensions had been performed by a number of investigators prior to World War II. In most of the early tests, a microscopic technique was used, but with the development of methods for producing larger yields of rickettsiae, macroscopic tests offered promise of practical application. Stuart-Harris and his associates,[42] using epidemic and murine suspensions prepared from the lungs of mice infected by the intranasal route, detected agglutinins in guinea pig and human convalescent sera. They concluded that differences between epidemic and murine typhus could be demonstrated by rickettsial agglutination. Van Rooyen and Bearcroft[43] were the first to employ suspensions of epidemic and murine typhus micro-organisms prepared from yolk-sac cultures and purified by the Craigie extraction technique. They used a macroscopic agglutination technique with sera from patients with typhus fever and concluded that a differential diagnosis between epidemic and murine typhus was possible with this test.

Plotz and Synder[44] undertook an evaluation of rickettsial agglutination with purified antigens similar to those employed in the complement fixation studies that have been described (p. 183). Again, the specimens tested consisted of the sera obtained from the 32 unvaccinated patients in Cairo. Agglutinins occurred in rising titer in all cases during the course of the disease. Table 26 summarizes the results in one of the patients. It may be seen that the titer obtained with epidemic typhus antigen exceeds that found with the murine typhus antigen, but there is more cross-reaction here than was noted in the complement fixation tests on the same specimens (table 22). In extending the test to sera from patients with other diseases, it was found that titers were obtained at times. These workers concluded, therefore: "Since epidemic and murine agglutinins may occur in convalescent specimens from cases of Rocky Mountain spotted fever, occasionally in high titer, caution should be observed in evaluation of this test when used as a diagnostic procedure."

Regrettably, routine rickettsial agglutination tests were not performed in the Cairo laboratory of the Typhus Commission partly because the procedure utilizes about 10 times the amount of antigen employed in complement fixation. In the vaccinated patients with epidemic typhus fever, the serological tests did not, therefore, include rickettsial agglutination. Data obtained in tests on sera from one such patient, however, are given in table 15 (case 3). In the section (p. 204) dealing with murine typhus, it

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[42] Stuart-Harris, C. H., Rettie, G. K. C., and Oliver, J. O.: Rickettsial Agglutination Studies in Typhus Fever. Lancet 2: 537-538, 30 Oct. 1943.

[43] Van Rooyen, C. E., and Bearcroft, W. G. C.: Typhus Rickettsial Agglutination Tests in the Middle East Forces and Egypt. Edinburgh M.J. 50: 257-272, May 1943.

[44] See footnote 32 (1) and (4), pp. 179–180.

TABLE 26.—*Rickettsial agglutination test results in case 1344—strain isolated*

Day of disease	Serum titer with—	
	Epidemic antigen	Endemic antigen
4th	0	0
5th	0	0
6th	0	0
8th	1:80	1:40
10th	1:640	1:160
12th	1:2, 560	1:160
14th	1:5, 120	1:1, 280
19th	1:10, 240	1:1, 280
20th	1:10, 240	1:1, 280
23d	1:10, 240	1:1, 280
25th	1:5, 120	1:640
27th	1:5, 120	1:640
115th	1:160	1:40
286th	1:80	1:10

Source: Plotz, H., and Snyder, J. M.: The Serological Pattern in Epidemic Typhus Fever. IV. Rickettsial Agglutination. Division of Virus and Rickettsial Diseases, Army Medical School, Army Medical Center, Washington, D.C., 1944. [Official record.]

has been suggested that the rickettsial agglutination test may be more specific in vaccinated individuals than is the complement fixation test.[45] Further information on the antibody responses of patients acquiring epidemic typhus fever after vaccination would be required to establish this point.

Neutralizing antibody test.—In 1940, Gildemeister and Haagen[46] described the association of a toxin with living murine typhus rickettsiae grown in yolk sacs of developing chick embryos. These workers were interested in producing a vaccine and, among other questions to be answered, wished to establish whether rickettsiae grown by this technique had kept their pathogenicity for white mice. Accordingly, they injected a suspension of yolk sac infected with *R. mooseri* intraperitoneally into white mice in 0.5 and 1.0 ml. amounts. To their surprise, all the mice died within 4 to 20 hours, some in convulsions. Further study of this finding revealed that this effect was due to the presence of a rickettsial toxin and that the toxin was destroyed by heating to 60° C., or by treating with formalin; that is, it was destroyed by procedures used to kill the rickettsiae. Finally, they demonstrated that convalescent serum from either epidemic or murine typhus would neutralize the toxin.

[45] Plotz, H., and Wertman, K.: Modification of Serological Response to Infection With Murine Typhus by Previous Immunization With Epidemic Typhus Vaccine. Proc. Soc. Exper. Biol. & Med. 59: 248-251, June 1945.

[46] Gildemeister, E., and Haagen, E.: Fleckfieberstudien. I. Mitteilung: Nachweis eines Toxins in Rickettsien-Eikulturen (Rickettsia mooseri). Deutsche Med. Wchnschr. 66: 878-880, 9 Aug. 1940.

Following the report of Gildemeister and Haagen, Bengtson and her coworkers [47] found that a toxic substance was present in yolk-sac cultures infected with epidemic typhus rickettsiae. Henderson and Topping [48] then showed that this toxic substance could be neutralized by convalescent epidemic typhus serum, and devised a neutralization test in mice which was adopted by the National Institutes of Health as the standard potency test for typhus vaccines. At about the same time, Hamilton [49] demonstrated that the toxins associated with suspensions of living epidemic and murine typhus rickettsiae were immunologically separable as were the antibodies that neutralized them.

Plotz and Bennett [50] undertook an evaluation of the mouse neutralization test as a possible laboratory tool for use in the diagnosis of typhus fever. Employing some 13,000 mice, they carried out neutralization tests on the serial serum specimens obtained from the 32 Cairo cases of epidemic typhus fever. In recording the results of this study, *complete protection* indicated that all mice tested at a given serum dilution survived; *partial protection*, that one or more but not all of the animals survived; and *no protection*, that all the mice in a group died. For uniformity in recording, the 50 percent end point of each titration was determined by the method of Reed and Muench. Table 27 illustrates the neutralization titers obtained in tests on sera from one of the Cairo cases. Actually, neutralizing antibody appeared during the course of illness in all of the cases studied; 28 percent developed neutralizing antibodies by the 6th day, 75 percent by the 8th day, and 100 percent by the 11th day. The curve of neutralizing antibody response was quite similar to that obtained in Weil-Felix *Proteus* OX-19 agglutination tests on the same sera.

Of additional interest were the results obtained by the same authors when epidemic typhus neutralization tests were performed with specimens of serum from cases of Rocky Mountain spotted fever. The patients from whom the specimens were obtained had not been given any typhus vaccine, nor did they have a history of typhus fever. Neutralizing antibodies for epidemic toxin were found, however, in 11 cases of Rocky Mountain spotted fever studied. This finding indicated that the epidemic neutralizing antibody was not restricted to epidemic typhus fever, and hence, these workers concluded that the mouse neutralization test is not reliable as an indication of a past infection with typhus.

Isolation and identification of *R. prowazeki* strains.—Isolation of the causative agent and identification of it through appropriate means is classically the only absolute method of diagnosis of an infectious disease. Strain

[47] U.S. Public Health Service, Federal Security Agency: National Institute of Health Bulletin No. 183. Studies of Typhus Fever. Washington: U.S. Government Printing Office, 1945, pp. 25-29.

[48] U.S. Public Health Service, Federal Security Agency: National Institute of Health Bulletin No. 183. Studies of Typhus Fever. Washington: U.S. Government Printing Office, 1945, pp. 41-56.

[49] Hamilton, H. L.: Specificity of the Toxic Factors Associated With the Epidemic and Murine Strains of Typhus Rickettsiae. Am. J. Trop. Med. 25: 391-395, September 1945.

[50] See footnote 32 (3), p. 179.

TABLE 27.—*Epidemic neutralizing antibody findings in case 1344—strain isolated*

Day of disease	50 percent end point titer final dilution	Day of disease	50 percent end point titer final dilution
4th	0	19th	2, 580
5th	0	20th	1, 444
6th	0	23d	1, 618
8th	25	25th	1, 618
10th	90	27th	722
12th	645	115th	161
14th	2, 048	286th	51

Source: Plotz, H., and Bennett, B. L.: The Serological Pattern in Epidemic Typhus Fever. III. The Neutralizing Antibody. Division of Virus and Rickettsial Diseases, Army Medical School, Army Medical Center, Washington, D.C., 1944. [Official record.]

isolation of *R. prowazeki* was, therefore, often performed in the field laboratories of the U.S.A. Typhus Commission in order to establish a firm basis for the observations made in their various investigations. In addition to the obvious importance of strain isolation for diagnostic purposes, it was also desirable for laboratory comparison of immunity relationships between strains that were isolated during epidemiological surveys in various parts of the world. Strains of *R. prowazeki* were also available for special vaccine production if differences in immunogenic properties from the Breinl strain (employed in the U.S. Army vaccine) had become manifest. Strains were used further in the laboratory evaluation of chemotherapeutic agents and in the preparation of antigens for serological tests.

Guinea pigs were, of course, invaluable in the initial isolation of typhus fever organisms, either from the ground clot of blood drawn from the patient early in the course of illness or from ground infected lice. The Cairo Unit of the Typhus Commission maintained a colony of noninfected lice for use in such studies.[51] Pill boxes containing approximately 200 lice each, and prepared with a fine-mesh cloth screen through which the lice could feed, were often carried by members of the Typhus Commission to distant points of survey. The lice were fed on their persons until such time as an appropriate case of suspected typhus fever was found. The pill box would then be attached with adhesive tape to the patient's leg for about 10 days. At the end of this feeding period, the louse box was carefully removed and sealed in an envelope, not to be opened again until the worker had returned to the laboratory, often hundreds of miles distant from the patient. At the laboratory, the material was carefully ground and injected into guinea pigs for the conventional isolation-of-strain procedure. In this manner, for

[51] Snyder, J. C., and Wheeler, C. M.: The Experimental Infection of the Human Body Louse, *Pediculus humanus corporis*, With Murine and Epidemic Louse-Borne Typhus Strains. J. Exper. Med. 82: 1-20, July 1945.

example, one officer [52] was able to isolate in Cairo 10 strains of *R. prowazeki* from partisan soldiers ill with typhus in Yugoslavia during March 1945.

Supplies of guinea pigs were limited so that field studies were often hampered. For this reason, the observation of Snyder and his coworkers [53] that two desert rodents, namely, *Gerbillus gerbillus* and *Gerbillus pyramidum*, were susceptible to experimental typhus infection proved to be valuable for the studies of the Typhus Commission in Cairo.

The developing chick embryo was employed for cultivation of *R. prowazeki* in large quantities for vaccine production and for antigens, as has been noted. However, the embryonated egg was not widely used for direct isolation of rickettsiae from the blood of patients ill with typhus fever, and the degree of successful strain isolation that might be achieved through this technique remains to be determined.

TREATMENT

The treatment of epidemic typhus fever may be considered in two broad categories. First are the general supportive measures including good nursing, particular attention to diet, fluids and electrolytes, and appropriate management of complications as they arise. These measures have been outlined (p. 153) with the observations and reasoning on which they were based, and need little exposition here.

Supportive therapy.—Diligent nursing care is required throughout the febrile period and also during convalescence. The position of semistuporous patients should be changed often to prevent both skin and pulmonary complications. The oral cavity should be cleansed frequently in an effort to prevent parotitis. Careful attention must be given to fluid intake and output. As much as 4,000 cc. of fluids may be required daily, preferably administered orally. Supplemental intravenous fluids should be given whenever necessary to maintain fluid balance. With respect to diet, high protein and caloric intake is associated with less loss of weight and a shorter period of convalescence. In severe cases, nourishing protein and carbohydrate mixtures may be given via an indwelling stomach tube. Delirium and extreme restlessness may be controlled by chloral hydrate or paraldehyde, but barbiturates act unpredictably.

The present discussion is chiefly concerned with specific treatment, including serotherapy, the use of antibiotics, and chemotherapy, and some consideration is given to prophylaxis.

Serotherapy.—Immune serum had been used by a number of workers in the treatment of louseborne typhus prior to World War II. Human con-

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[52] Memorandum, Maj. Chris J. D. Zarafonetis, MC, to Brig. Gen. S. Bayne-Jones, Director, U.S.A. Typhus Commission, 27 Apr. 1945, subject: Typhus Strains from Yugoslavia.

[53] Snyder, J. C., Zarafonetis, C. J. D., and Liu, W. T.: The Susceptibility of the Rodents, *Gerbillus gerbillus* and *Gerbillus pyramidum*, to Experimental Typhus Infection. Proc. Soc. Exper. Biol. & Med. 59: 110-112, June 1945.

valescent serum generally showed no noticeable effect on the course of the disease, while there were conflicting reports regarding the efficacy of sera obtained from animals that had recovered from experimentally induced typhus. With improved techniques for the growth of large quantities of rickettsiae, however, the hyperimmunization of animals was facilitated. Refined, concentrated antityphus serum was prepared from rabbits hyperimmunized with suspensions of infected yolk sacs of developing chick embryos.[54] Serum prepared in this manner was shown to have a strikingly protective effect in experimental typhus.[55]

Knowledge of this laboratory experience prompted Yeomans, Snyder, and Gilliam[56] to undertake a clinical trial of hyperimmune rabbit serum in patients admitted to the ward of the Typhus Commission at the Cairo Fever Hospital. This study was begun in April 1943; 25 patients with typhus were treated. All were skin tested for sensitivity to the serum, and, if negative, serum therapy was administered. The total amount of serum given to each varied from 51 to 512 cc., with an average dose of 186 cc. for this group of patients.

Therapeutic effectiveness of hyperimmune rabbit serum was found to be related to the duration of illness at the time treatment was instituted. The results in 10 patients treated on the second and third day of the disease were almost uniformly good. The 15 patients who had been sick for 4, 5, or 6 days before serum was given did not show a striking difference in clinical severity from the "untreated" controls, except that there were no fatal cases. Of the 25 patients who received hyperimmune rabbit serum, 7 developed mild serum sickness.

Another opportunity to test the efficacy of serum therapy presented itself to the U.S.A. Typhus Commission group working at the Dachau Concentration Camp in May and June 1945.[57] Ten patients admitted to the Commission ward were given hyperimmune antityphus rabbit serum on the following dosage schedule: In the first 24 hours after admission, 0.5 cc. per pound of body weight; on the second and third days, 0.25 cc. per pound of body weight. All of the serum was injected intramuscularly in the buttocks after appropriate skin testing. Owing to limited supply, the average amount administered to these subjects was less than was given to the patients in the Cairo series. This may be the explanation for results less impressive than those obtained in the Cairo study. The illness in four patients was mild; four were moderately ill; and one was severely ill. The 10th patient treated died of widely disseminated tuberculosis 4 weeks after the

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54 Kurotchkin, T. J., van der Scheer, J., and Wyckoff, R. W. G.: Refined Hyperimmune Rickettsial Sera. Proc. Soc. Exper. Biol. & Med. 45: 323, October-December 1940.

55 Wyckoff, R. W. G., and Bohnel, E.: Therapeutic Effect in Guinea Pigs of Hyperimmune Epidemic Typhus Antiserum. Proc. Soc. Exper. Biol. & Med. 49: 712–715, April 1942.

56 Yeomans, A., Snyder, J. C., and Gilliam, A. G.: The Effects of Concentrated Hyperimmune Rabbit Serum in Louse Borne Typhus. J.A.M.A. 129: 19–24, 1 Sept. 1945.

57 See footnote 14, p. 155.

onset of typhus fever. The average duration of fever in the treated cases was 15.2 days as opposed to 16.2 days in 121 "untreated" control cases. Serum sickness appeared in 5 of the 10 patients treated.

It is of interest to observe that the hyperimmune serum did not have a rickettsiocidal effect, for Plotz and his coworkers [58] isolated rickettsiae from 11 of the Cairo patients after the serum had been given. From the prolonged incubation periods noted in isolating these micro-organisms in guinea pigs, it was postulated that the serum may have exerted a rickettsiostatic effect. Finally, these workers suggested that the beneficial clinical effect attributed to hyperimmune rabbit serum was due to its ability to neutralize the toxic substance elaborated by typhus rickettsiae.

Antibiotics.—In 1944, crude commercial penicillin was shown to inhibit the growth of typhus rickettsiae in the yolk sac [59] and markedly to reduce, or even completely prevent, mortality from murine typhus infection in mice.[60] Clinical trials of penicillin, however, were limited in both the number of cases treated and the dosages administered. For example, Col. William S. Stone, MC, Chief, Preventive Medicine, Medical Section, North African Theater of Operations, U.S. Army, and Captain Woodward of the Typhus Commission made available to British workers in Italy [61] 4 million Oxford units of penicillin for trial in the treatment of epidemic typhus fever. Four patients were treated, none before the sixth day of disease. The total amount of penicillin dosage ranged from 509,000 units to 800,000 units. Two of the four patients died.

Penicillin was given to four additional cases of epidemic typhus fever on the Typhus Commission ward in Cairo.[62] Yeomans and his coworkers could not determine on the basis of this limited experience whether penicillin given early, and in what were then considered "large amounts," did or did not affect the course of typhus. The potential usefulness of penicillin for the treatment of secondary bacterial infections superimposed on typhus fever, however, was recognized by them soon after this antibiotic became available.

Postwar studies by Greiff and Pinkerton [63] with pure crystalline penicillin fractions revealed important differences in the rickettsiostatic activity of the different fractions. Penicillin X was about four times as effective on a unit basis as pencillin G, and there were differences in the potency of other fractions. From this, it would appear that the irregular results reported

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58 Plotz, H., Bennett, B. L., and Tabet, F.: Effect of Concentrated Hyperimmune Rabbit Serum on Circulating Agent in Louse Borne Typhus. Proc. Soc. Exper. Biol. & Med. 63: 176–178, October 1946.

59 Greiff, D., and Pinkerton, H.: Inhibition of Growth of Typhus Rickettsiae in the Yolk Sac by Penicillin. Proc. Soc. Exper. Biol. & Med. 55: 116–119, February 1944.

60 Moragues, V., Pinkerton, H., and Greiff, D.: Therapeutic Effectiveness of Penicillin in Experimental Murine Typhus Infection in dba Mice. J. Exper. Med. 79: 431–437, April 1944.

61 Medical Research Council, Special Report Series No. 255, Chemotherapeutic and Other Studies of Typhus. London: His Majesty's Stationery Office, 1946, pp. 78–81.

62 See footnote 6, p. 147.

63 Greiff, D., and Pinkerton, H.: The Rickettsiostatic Action of Crystalline Penicillin Fractions in Embryonate Eggs. Proc. Soc. Exper. Biol. & Med. 68: 228–232, June 1948.

could have been due to varying proportions of the penicillin fractions in the preparations used. These workers concluded that the clinical trials referred to above were invalidated by the use of low doses, started late in the course of the disease, by the small number of cases, and by the fact that fractions of proved potency against *R. prowazeki* were not employed. The effectiveness of penicillin in human rickettsial infection, therefore, remained undetermined.

The newer broad-spectrum antibiotics were not discovered until after the period under review and so are not included here, but their importance will be indicated at the end of the discussion of therapy.

Chemotherapy.—A new chapter in the treatment of epidemic typhus fever and other rickettsial diseases was begun during World War II with the observation that PABA exhibited antirickettsial activity in vivo. This was discovered independently by Snyder, Maier, and Anderson in 1942 [64] and by Greiff, Pinkerton, and Moragues in 1944.[65] Its use was suggested to the former group by the apparently deleterious effect of sulfonamides on the course of experimental typhus infection and the knowledge that PABA and sulfonamides are metabolic antagonists. The second group of workers first tried PABA in an effort to enhance the action of penicillin. Still a third discovery of the inhibitory effect of PABA on the growth of typhus rickettsiae was made in 1944 by Takemori, working at the Hygienic Institute in Dairen, Manchuria.[66]

The letter report of Snyder and his associates was circulated in laboratories known to be concerned with rickettsial diseases. At the Army Medical School, Hamilton, Plotz, and Smadel [67] undertook a systematic study of the effect of PABA and related substances on the growth of rickettsiae. Inoculating the test compound directly into the yolk sacs of infected chick embryos, which were allowed to develop until death resulted from rickettsial infection, they found a marked difference in survival time of the treated eggs as compared with the controls (chart 9). In addition, it was shown by direct count of rickettsiae in eggs, opened after an arbitrary period of time, that their numbers had been greatly reduced in those treated with PABA in comparison with the relatively rich growth in the controls.

The percentage of embryos protected with 2 mg. of PABA was, in general, higher than when 4 mg. (approximately 70 mcg/ml.) was used,

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[64] Letter, J. C. Snyder, John Maier, and C. R. Anderson, International Health Division, The Rockefeller Foundation, to Division of Medical Sciences, National Research Council, 26 Dec. 1942, subject: [Report on Chemotherapy of Typhus Fever].

[65] Greiff, D., Pinkerton, H., and Moragues, V.: Effect of Enzyme Inhibitors and Activators in the Multiplication of Typhus Rickettsiae. I. Penicillin, Para-Aminobenzoic Acid, Sodium Fluoride, and Vitamins of the B Group. J. Exper. Med. 80: 561–574, December 1944.

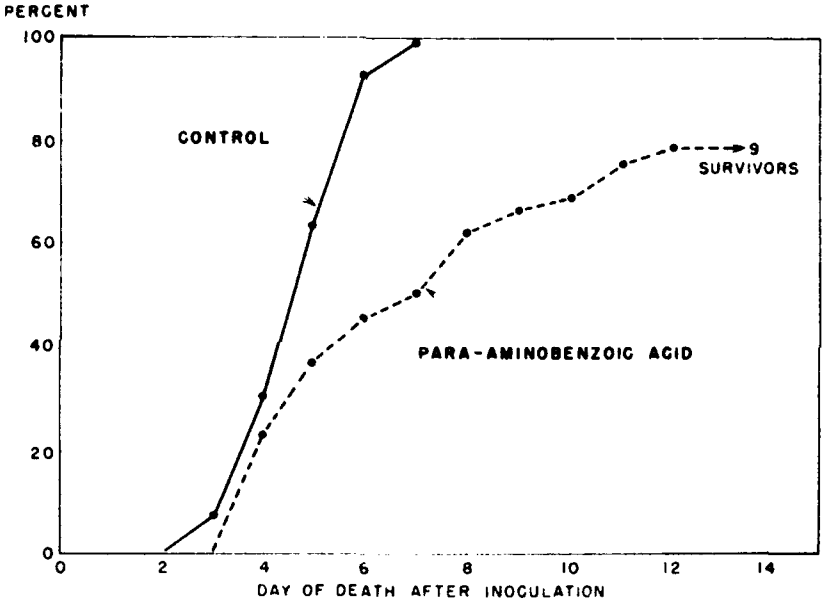
[66] Takemori, N.: The Actions of Sulfonamide Compounds and *p*-Aminobenzoic Acid on the Virus of Lymphogranuloma Inguinale and Typhus Rickettsiae in Vitro. Japanese Med. J. 2: 1–8, February 1949.

[67] Hamilton, H. L., Plotz, H., and Smadel, J. E.: Effect of p-Aminobenzoic Acid on the Growth of Typhus Rickettsiae in the Yolk Sac of the Infected Chick Embryo. Proc. Soc. Exper. Biol. & Med. 58: 255–262, March 1945.

suggesting a toxic effect of excessive PABA. Even so, the necessity for using quantities of PABA up to 2 mg. to inhibit rickettsial growth in an egg suggested the possibility that a nonspecific effect might be involved. Accordingly, two isomers, ortho- and meta-aminobenzoic acid, as well as acetyl-p-aminobenzoic acid (both sterilized by heat and sterilized by Seitz filtration), sulfanilamide, sodium benzoate, and benzoic acid were tested in concentrations equivalent to the maximal dose of PABA (4 mg. per egg). With the exception of the heat-sterilized acetyl derivative, none of these substances had any apparent effect on either the time of death or the number

CHART 9.—*Effect of para-aminobenzoic acid on time of death in chick embryos infected with* Rickettsia prowazeki

[Cumulative percent of dead embryos]



Source: Hamilton, H. L., Plotz, H., and Smadel, J. E.: Effect of p-Aminobenzoic Acid on the Growth of Typhus Rickettsiae in the Yolk Sac of the Infected Chick Embryo. Proc. Soc. Exper. Biol. & Med. 58: 255-262, March 1945.

of rickettsiae. Heating hydrolyzes a certain portion of acetyl-PABA into PABA, which is the probable explanation for the above observation. These studies clearly indicate that the inhibition of growth by PABA is due to a specific action of the drug.

An outstanding series of investigations by Greiff [68] and his colleagues shed further light on the mechanism of action of PABA in rickettsial infections, as shown by Greiff in the discussion which follows.

The rickettsiostatic action of para-aminobenzoic acid, first observed by Snyder and his co-workers in mice, later confirmed in the yolk sac by Hamilton and others and still later (because of war-time secrecy) observed independently in our laboratory, is a rather

68 (1) See footnote 65, p. 195. (2) Greiff, Donald: Biology of the Rickettsiae. *In* Rickettsial Diseases of Man. Washington: American Association for the Advancement of Science, 1948, pp. 51-63.

striking example of the inhibition of an intracellular parasite by a compound usually regarded as a vitamin. Pinkerton and Bessey showed that in riboflavin-deficient rats, practically moribund from typhus, riboflavin had a striking "chemotherapeutic" action, causing rapid recovery from what appeared to be overwhelming and certain fatal infection. With the sudden resumption of cellular respiration when the missing link is furnished, the normal resistance of the rat is restored. With this fact in mind we have been interested in learning the mechanism of action of PABA, and particularly in determining whether or not this compound like other compounds and conditions found to discourage rickettsial growth, causes an increase in the cellular metabolic rate.

In conjunction with our earlier work, we proved conclusively that cyanide had no effect on the rickettsiostatic action of PABA. From this fact we concluded that PABA either acted directly on the rickettsiae, in a manner similar to the action of sulfadrugs on bacteria, or that PABA, like toluidine blue, increased cell respiration by short-circuiting the cyanide sensitive system of respiratory enzymes.

Recently we have developed a reliable method for measuring the oxygen consumption and carbon dioxide output of fertile eggs. In 3 separate experiments, we have found that the injection of PABA into the yolk sac markedly increases the oxygen consumption. The effect is noted after a delay of about 5 days, which is perhaps caused by slow absorption of the precipitated compound from the yolk sac. From the 5th to the 10th days after injection (almost exactly the period of active rickettsial multiplication) the oxygen consumption continues to be 25–50 percent above that of the uninjected control eggs. This of course does not prove that the rickettsiostatic action of PABA is due solely to its indirect action in increasing cellular respiration, but in view of the facts previously brought out, this seems to be a reasonable assumption.[69]

Greiff commented further in summarizing the work of his group:

Conditions such as low temperature and riboflavin deficiency, which decrease the rate of cellular metabolism, favor the growth of rickettsiae. Higher temperatures and certain dyes and other agents which increase cellular metabolism are unfavorable to rickettsial growth. Our experiments indicate that the activity of the cyanide sensitive respiratory enzyme (cytochrome oxidase) is one essential factor in the protection of cells against rickettsial multiplication. In the case of toluidine blue and para-aminobenzoic acid, however, rickettsiostatic activity is correlated with increased cellular respiration brought about by mechanisms which are cyanide-insensitive.

Clinical studies designed to determine the therapeutic effect of PABA in epidemic typhus fever were begun on the ward of the Cairo Unit of the Typhus Commission in 1943. Yeomans, Snyder, Murray, Zarafonetis, and Ecke [70] were able to report in 1944 that the drug had a favorable influence on the clinical course of patients whose treatment was begun in the first week of the disease. These studies were continued through 1945, both in Cairo and at the Dachau Concentration Camp,[71] and a summary of the results of treatment of a cumulative total of 95 patients suffering from typhus fever was later issued.[72]

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[69] Recent observations indicate that PABA enhances monamine oxidase activity. This may represent the pathway through which increased oxygen uptake is mediated by PABA.

[70] See footnote 6, p. 147.

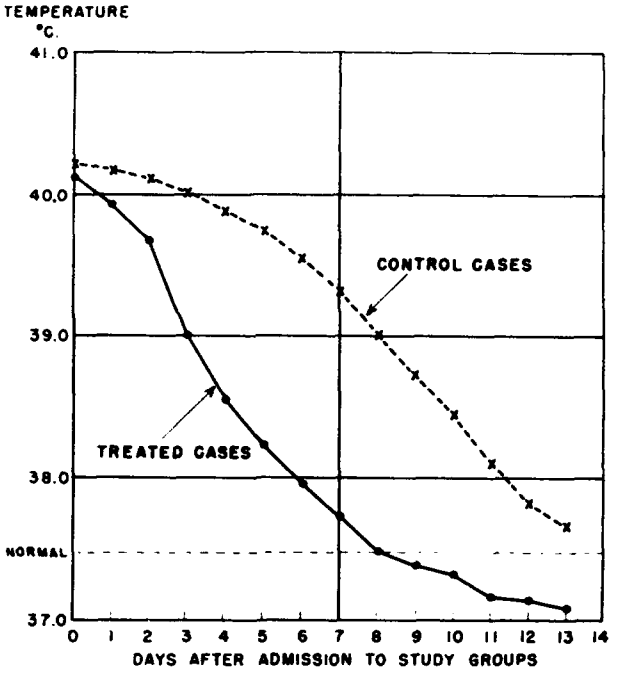
[71] See footnote 14, p. 155.

[72] Snyder, J. C., Yeomans, A., Clement, D. H., Murray, E. S., Zarafonetis, C. J. D., and Tierney, N. A.: Further Observations on the Treatment of Typhus Fever With Para-Amino-Benzoic Acid. Ann. Int. Med. 27: 1–27. July 1947.

The most carefully controlled observations were made in Cairo. Here, patients were placed alternately in control and PABA-treated groups. The study groups were composed of 39 male Egyptian patients, ages 18 to 48, suffering from epidemic typhus fever. The diagnosis was based on the clinical course, serological findings, and, in 19 instances, isolation of *R. prowazeki* from the blood or from normal lice fed on the patients during the febrile period. None of the patients had been vaccinated against typhus fever or gave a history of a previous attack of the disease. Most were somewhat

CHART 10.—*Comparison of temperatures of 20 para-aminobenzoic acid treated patients and 19 alternate control patients, Cairo, Egypt, 1944 and 1945*

[Mean daily rectal temperatures are plotted for each group, zero day being the day of admission of each patient to the study (the mean duration of illness at the time of admission for both groups was 4.4 days). The temperatures of fatal cases are included up to the last reading before death occurred]



Source: Snyder, J. C., Yeomans, A., Clement, D. H., Murray, E. S., Zarafonetis, C. J. D., and Tierney, N. A.: Further Observations on the Treatment of Typhus With Para-Amino-Benzoic Acid. Ann. Int. Med. 27: 1-27, July 1947.

underweight but appeared to be in good physical condition otherwise. A few of the patients were subsequently found to have subclinical schistosomiasis, but none was excluded because of this finding. One PABA-treated patient developed an exacerbation of amebic dysentry during convalescence from typhus, but his case was included in the results. The patients were in the first week of illness when they were placed in the control and PABA-treated groups in automatic rotation.

In the 19 control subjects, mean values were as follows: Age, 27.9 years; duration of illness when admitted to the group, 4.4 days; duration of fever,

17.9 days (chart 10). The incidence of complications was higher in this group, and there were six fatal cases.

In the 20 patients treated with PABA, mean values were as follows: Age, 28.5 years; duration of illness when treatment was started, 4.4 days; duration of fever, 12.8 days. The incidence of complications was less than in the control group, and there was one death in this series.

The treatment regimen to be followed with PABA was evolved only after considerable experimentation. Yeomans and his coworkers[73] outlined the plan of therapy, as follows:

> In all instances, PABA was administered by mouth. The initial dose varied from 4 to 8 gm. In the majority of cases, the initial dose was followed by 2 gm. every 2 hours unless the concentration in the blood attained excessive values. Adjustments in dosage were made in relation to fluid intake and urinary output. The fluid intake in nearly all instances was adequate to maintain the output of urine between 1,500 and 3,000 cc. in 24 hours.
>
> The effort was made to keep the concentration of PABA in the blood between 10 and 20 mg. per 100 cc. PABA is absorbed and excreted very rapidly, so that a 2-hourly schedule of administration was decided on as that most likely to produce a relatively constant blood level. Determinations made at various times during treatment indicated that the 2-hourly schedule was effective in maintaining a satisfactory concentration of PABA throughout the period of therapy.
>
> PABA was continued for varying lengths of time in the first cases. Subsequently, it was decided that treatment should be continued until the patient's rectal temperature was 37.5° C. (99.5° F.) or less for 24 hours. The average amount of PABA for each case was approximately 127 gm. The patients who are the subject of discussion in this study received PABA for at least 3 days.
>
> Nausea and vomiting attributable to PABA occurred in the first few cases. Thereafter, in order to lessen gastric irritation, sufficient sodium bicarbonate was given to neutralize the PABA. The acidity of the urine was determined at least once daily during therapy. The amount of sodium bicarbonate was varied as required to keep the urine approximately neutral in reaction. After this plan was adopted, vomiting was encountered very infrequently.
>
> PABA was available in tablets of 0.5 gm. each and in capsules of 0.3 gm. each. Neither form was suitable for administration to typhus patients, who could not be persuaded to swallow the large numbers of tablets or capsules required for each dose, but they took powdered PABA readily if it was suspended in water or partially dissolved in a sufficient volume of 5 percent sodium bicarbonate solution to render the mixture slightly alkaline. The usual amount was 2 gm. of powdered PABA with 25 cc. of sodium bicarbonate solution.[74] After swallowing the mixture, the patient was quickly given water to take away the slightly unpleasant taste of the drug. This method of administration was entirely satisfactory in most instances.

Premature withdrawal of PABA therapy was followed by a mild febrile period which probably represented a mild recrudescence of the disease. For

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[73] See footnote 6, p. 147.

[74] Postwar experience in the treatment of hundreds of nontyphus patients has shown that a chilled, 10 percent aqueous solution of pure prescription-grade potassium para-aminobenzoate (Potaba) is much more readily tolerated than the relatively crude mixtures employed during these typhus studies. In retrospect, it would seem that even better results could be achieved in typhus with Potaba if the need should ever arise again.

this reason, it was found advisable to continue the initial course of PABA for 48 hours after the patient's temperature had returned to normal.

At no time were crystals of PABA ever noted in the urine of the patients treated. There was detected, however, a slight tendency to leukopenia during this form of therapy. Snyder and his coworkers [75] found the mean of the lowest counts was 5,200 per cubic millimeter for 19 control patients, while the mean for the 20 patients treated with PABA was 4,100 per cubic millimeter, but the difference was not statistically significant. Analysis of the differential leukocyte counts did, however, reveal a slight but statistically significant reduction in the percentage of segmented neutrophils (69.9 percent was the mean for the controls, and 55.1 percent was the mean for the treated group) and an increase of a similar percentage in the lymphocytes. The differences in percentages of monocytes, eosinophils, and basophils were not significant. Although slight depression of the neutrophils was attributable to the administration of PABA, no instance of true agranulocytosis was encountered in these studies.

PABA was thus discovered to have important antirickettsial activity and, through studies as just described, was brought to the position of a safe and promising drug for clinical use during World War II. Its importance in the management of epidemic typhus fever and other rickettsial diseases was short lived as a result of the postwar development of broad-spectrum antibiotics.[76] The wartime studies with PABA may yet be shown, however, to have great significance both from the standpoint of rickettsial growth factors and as a clue to certain intracellular metabolic processes.

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[75] See footnote 72, p. 197.

[76] PABA has since been supplanted by the broad-spectrum antibiotics, which have greatly simplified the treatment of epidemic typhus fever. Properly used, these will reduce the mortality of the disease very nearly to zero. Chloramphenicol, Aureomycin (chlortetracycline), and Terramycin (oxytetracycline) are all effective, and usually bring about dramatic improvement within 24 to 72 hours after institution of therapy. Woodward and Parker (Woodward, Theodore E., and Parker, Robert T.: Clinical Application and Mode of Action of Antibiotics in Rickettsial and Virus Diseases. *In* The Dynamics of Virus and Rickettsial Infections. New York: The Blakiston Company, Inc., 1954, pp. 437–457.) consider the following dosage schedules to be optimal. For chloramphenicol, the initial oral dose is 50 mg. per kilogram of body weight, and for Aureomycin and Terramycin, 25 mg. per kilogram of body weight is given. Maintenance doses are calculated on the basis of 50 mg. per kilogram per day for chloramphenicol, and 25 mg. per kilogram per day for Aureomycin and Terramycin. The total daily requirement is given in equally divided doses at 6- to 8-hour intervals. Administration of the antibiotic employed is continued until the patient has improved and has been afebrile for about 24 hours. When oral medication is not feasible, the intravenous route may be used. The initial dose of chloramphenicol should be calculated on the basis of 20 mg. per kilogram of body weight, and Aureomycin and Terramycin on the basis of 5 to 10 mg. per kilogram of body weight. Subsequent daily requirements are calculated in the same manner, divided into four equal doses which are administered at 6-hour intervals. Undesirable side effects such as nausea, vomiting, glossitis, diarrhea, and proctitis are more commonly encountered with Aureomycin and Terramycin than with chloramphenicol. The newer related antibiotic, terracycline, appears to be equally effective with less toxicity. There have been no reports of hemopoietic depression from the short-term use of chloramphenicol in rickettsial diseases.

Cortisone has been combined with broad-spectrum antibiotic therapy in rickettsial diseases. Headache was promptly relieved, toxicity disappeared, the appetite returned, and the fever lasted less than 2 days on average. The addition of cortisone to the treatment regimen should especially be considered in late, severely ill, extremely toxic patients.

Prophylaxis.—Prevention of epidemic typhus fever was made practicable during World War II with the production of adequate quantities of a potent vaccine and by improved methods of louse control.

Personnel in the Armed Forces of the United States were vaccinated with antityphus vaccine of the Cox type. Although 104 cases of epidemic typhus were detected in U.S. troops, there was not a single death. Typhus contracted after vaccination is, therefore, relatively mild and rarely if ever causes death. Furthermore, lice fed on patients who were vaccinated before acquiring typhus develop very few rickettsiae in comparison to lice fed on unvaccinated patients. Thus, vaccination not only alters the susceptibility of the individual but, when used on a broad scale, also serves to reduce the epidemic potential of the disease.

In the complementary effort to prevent the disease by destroying the vector, a number of agents were developed, the most effective being DDT (dichlorodiphenyltrichloroethane). A 10 percent DDT powder dusted into the clothing was found to provide almost complete protection against lice for 3 weeks or more.[77] DDT or other insecticide powders are of greatest importance when conditions prevail which are favorable for an epidemic. During World War II, the vigorous application of delousing measures in the prevention or prompt control of typhus epidemics was an historic accomplishment in the annals of preventive medicine.[78]

Part II. Brill's Disease

It is now recognized that Brill's disease is clinical recrudescence of a previous epidemic typhus infection. The causative micro-organism, *R. prowazeki*, may remain latent in an individual for years following the original infection. As immunity wanes, and possibly influenced by still undetermined factors, the rickettsiae are activated and give rise to illness which often resembles that associated with the primary infection.

HISTORICAL NOTE

Nathan Brill first described the disorder in 1898 and again in 1910 as an acute infectious disease of unknown origin. His reports were based on the study of 221 cases occurring sporadically in New York City during more than a decade of observation. Brill's clinical description is classic. He also noted that Widal tests and blood cultures were negative and called attention to the similarity of the disease to typhus fever.

Additional cases were soon reported by others, and in 1912, Anderson and Goldberger showed by cross-immunity tests that Brill's disease was

[77] Some strains of lice encountered during the recent Korean conflict, however, were DDT resistant (Hurlbut, H. S., Altman, R. M., and Nibley, C., Jr.: DPT Resistance in Korean Body Lice. Science 115: 11-12, 4 Jan. 1952).

[78] See footnote 4, p. 144.

related to Mexican typhus. At that time, it was believed that there was only one form of typhus fever, but during the next 30 years, it was clearly established that there were two distinct varieties; namely, louseborne epidemic typhus and fleaborne murine typhus. In the absence of epidemiological evidence incriminating either lice or fleas, however, the position of Brill's disease remained uncertain until Zinsser offered an explanation in 1934. On epidemiological grounds, Zinsser postulated that Brill's disease resulted from recrudescence of an old typhus infection which had been acquired in Europe. This theory was further supported by the fact that three strains of rickettsiae which he and Castaneda had recovered from patients with Brill's disease gave biological reactions similar to those induced by *R. prowazeki*.

EPIDEMIOLOGY

Brill's disease occurs sporadically and infrequently among individuals who have previously had epidemic typhus fever. The original infection may have been acquired from a few years to as long as 50 years or more in the past. Subjects who continue to live in typhus zones may serve as the interepidemic reservoir of epidemic typhus fever.[79] On the other hand, Brill's disease in individuals who have migrated to nontyphus areas presents no epidemic problem. The incidence of Brill's disease is not known, but it is very small in proportion to the total number of cases of epidemic typhus fever.

CLINICAL PICTURE

The typical case resembles a mild to moderately severe attack of epidemic typhus fever as described in the preceding section. All of Brill's original cases exhibited a rash, as it was a required feature for diagnosis. It is now recognized, however, that many mild cases occur without an eruption at any time during the course of illness.

The febrile course varies from a few days in mild cases to 2 weeks or more in severe attacks. If an eruption is present, it may be sparse and evanescent or it may be moderately extensive. Headache and malaise persist until the fever subsides. The mortality is low, possibly 1 or 2 percent. The great majority of patients have a prompt convalescence and complications are rare.

DIAGNOSIS

The clinical diagnosis of Brill's disease may be made in a patient who has lived at some previous time in an epidemic typhus area and whose illness is characterized by fever, intense headache, and a maculopapular rash ap-

[79] In this connection, it has been shown that lice fed upon patients during the first week of Brill's disease become readily infected with *R. prowazeki* and, therefore, could initiate an epidemic under suitable conditions (Murray, E. S., and Snyder, J. C.: Brill's Disease. II. Etiology. Am. J. Hyg. 53: 22–32, January 1951).

pearing on the fourth to sixth day of disease. In cases without a rash, the remaining criteria should lead to the consideration of Brill's disease in the differential diagnosis.

From the foregoing, it is evident that the specific diagnosis of Brill's disease must rest on other than clinical findings alone. In this area, Col. Harry Plotz, MC, made a highly significant contribution during World War II,[80] demonstrating that complement fixation tests with purified rickettsial antigens could be applied to the specific diagnosis of epidemic typhus and murine typhus. The following serological evidence substantiates this point of view:

In 23 cases of Brill's disease examined all showed a positive complement fixation with an epidemic rickettsial antigen. In 10 cases there was fixation with an epidemic rickettsial antigen and no fixation with an endemic rickettsial antigen. In 13 cases there was some cross-fixation but in all instances where this occurred the titer obtained was higher with epidemic antigen. The pattern of fixation in this disease resembles that obtained in epidemic typhus fever.

Absorption tests were performed on specimens of serum from Brill's disease where cross-fixation had occurred. An endemic rickettsial antigen removed all the endemic antibody with slight effect upon the titer of epidemic antibody. On the other hand, a similar treatment of the serum with an epidemic rickettsial antigen resulted in the removal of both the epidemic and endemic antibody; no selectivity of absorption was observed. These results would indicate that the endemic rickettsial antigen pattern was different from that of the antigenic pattern of the epidemic strain. The removal unselectively of both endemic and epidemic antibodies by the epidemic antigen suggests that the latter may be a more complete or complex antigen than the endemic antigen.

The results obtained in Brill's disease are highly significant for the epidemiology of typhus fever. They would indicate that mild cases of epidemic typhus actually exist in the United States. The disease is not transmitted from person to person in this country simply because the louse vector is not present. Furthermore, these results indicate that one attack of typhus does not confer a lifelong immunity as is generally believed. The virus is probably harbored in the body and when the resistance is lowered the virus multiplies and induces a mild attack. If these cases should occur in a louse-infested community the disease might readily spread from person to person. The observations on Brill's disease strongly suggest that man serves as the reservoir for epidemic typhus between outbreaks just as the rat does in endemic typhus.

Plotz further stated: "The complement fixation test now provides a tool with which surveys of the prevailing types of typhus in a region can be determined." [81]

Thus, recrudescence of rickettsial activity occurs unpredictably in a small percentage of persons who have had epidemic typhus fever. The factors which give rise to this phenomenon are not known, so that the specific

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[80] Plotz, H: Complement Fixation in Rickettsial Diseases. Science 97: 20-21, 1 Jan. 1943.

[81] It should be noted that while agglutinins for suspensions of *Proteus* OX-19 develop almost uniformly during initial attacks of epidemic typhus fever, a similar response is often lacking during the recrudescent disease (Murray, E. S., Pšorn, T., Djaković, P., Sielski, S., Broz, V., Ljupsa, F., Gaon, J., Pavlević, R., and Snyder, J. C.: Brill's Disease. IV. Study of 26 Cases in Yugoslavia. Am. J. Pub. Health 41: 1359-1369, November (Pt. 1) 1951). This is comparable to the *Proteus* OX-K findings in second attacks of scrub typhus.

prevention of Brill's disease is not feasible at this time. Fortunately, other measures kept the incidence of epidemic typhus fever in our troops to a minimal level and, thereby, reduced the likelihood of Brill's disease in them to zero. The importance of Brill's disease to the U.S. Army Medical Service, therefore, lies in its epidemiological implications among civilians in oversea areas where our forces may be stationed.

Part III. Endemic (Murine) Typhus

Endemic or murine typhus is an acute febrile illness caused by infection with *R. mooseri* (syn. *Rickettsia typhi*) transmitted to man by rat fleas. Many of the terms applied to louseborne typhus have also been used in the past in referring to cases of endemic typhus. Clinically, the disease is similar to epidemic typhus, but it usually runs a milder course.

Probably the first clinical description was written in 1913 by Paullin who recognized a mild form of typhus fever occurring in Atlanta, Ga. The recognition of murine or endemic typhus as a separate entity from epidemic typhus fever and Brill's disease, however, was not made until some years later. An important advance was made by Neill in 1917. He noted that scrotal swelling was produced in male guinea pigs by the intraperitoneal injection of blood obtained from cases of typhus fever in Texas. Mooser extended observations along this line in 1928 and emphasized that this biological reaction was characteristic for a Mexican strain of typhus.[82] In contrast, scrotal swelling was not a feature in guinea pigs infected with strains of classical or louseborne typhus rickettsiae. Meanwhile, Maxcy and Havens conducted extensive epidemiological studies on the typhus cases which occurred in the Southern and Southeastern United States. On the basis of these investigations, Maxcy, in 1926, postulated a rodent reservoir for this form of typhus, and suggested that transmission of the disease to man was accomplished by fleas.[83] This theory was confirmed in 1931 by Dyer and his associates who isolated the causative micro-organism from rat fleas obtained at a typhus focus in Baltimore, Md.[84]

EPIDEMIOLOGY

Murine typhus occurs as a natural infection of rats and certain other rodents in many parts of the world. The infection appears to be transmitted

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[82] Mooser, H.: Experiments Relating to Pathology and Etiology of Mexican Typhus (Tabardillo). I. Clinical Course and Pathologic Anatomy of Tabardillo in Guinea Pigs. J. Infect. Dis. 43: 241-260, September 1928.

[83] Maxcy, K. F.: An Epidemiological Study of Endemic Typhus (Brill's Disease) in the Southeastern United States. Pub. Health Rep. 41: 2967-2995, 24 Dec. 1926.

[84] Dyer, R. E., Rumreich, A., and Badger, L. F.: Typhus Fever; A Virus of the Typhus Type Derived From Fleas Collected From Wild Rats. Pub. Health Rep. 46: 334-338, 13 Feb. 1931.

among rodents by fleas, lice, and mites. The rat flea, *Xenopsylla cheopis*, is the principal vector involved in human infections. The causative microorganism, *R. mooseri*, may persist for long periods of time in the brain tissues of reservoir hosts. Similarly, it has been shown that once fleas have become infected, their feces may contain rickettsiae for at least 52 days and presumably for the remainder of their lives. Rickettsiae present in dry flea feces may remain infectious for long periods of time.

Human infections are acquired through the rubbing of infected feces into the fleabite wound or into an abrasion from scratching. Infection may also result from ingestion of food contaminated by infected flea feces or rat urine and from contamination of the oral or nasal mucosa with these excreta.

Cases of murine typhus occur sporadically throughout the world. In the United States, about 97 percent of the cases have been reported from Alabama, Georgia, Florida, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, and Texas (fig. 33).[85] Other foci of importance are the New York City area, N.Y., Los Angeles County, Calif., Norfolk area, Va., and Pulaski County, Ark. Murine typhus is encountered in port cities and in rural areas south of 33° N. latitude. Below this line, the long warm season and field storage of crops permit rats to live and multiply outdoors throughout most of the year, thereby enhancing the epidemiological potential for this disease. Although approximately 300 cases were reported in the United States in 1931, the number later increased greatly and reached a peak of 5,353 in 1944 (chart 11).

CLINICAL EXPERIENCE

Murine or endemic typhus was not an item of diagnosis in the U.S. Army medical statistics until 1940; all forms of typhus were included in a single figure prior to that time. From a practical standpoint, therefore, the experience of the U.S. Army Medical Department with murine typhus did not become meaningful until 1940 and thereafter.

During World War II, there were 787 cases of murine typhus in the U.S. Army (table 28). Fifteen fatalities were attributed to this infection. It is surprising that U.S. Army troops experienced a much greater incidence of fleaborne typhus than of the louseborne disease. Bayne-Jones has discussed in detail the basis for the less effective control measures of murine typhus during the period under review.[86]

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[85] Bradley, George H., and Wiley, John S.: The Control of Murine Typhus in the United States. *In* Rickettsial Diseases of Man. Washington: American Association for the Advancement of Science. 1948, pp. 229-240.

[86] See footnote 4, p. 144.

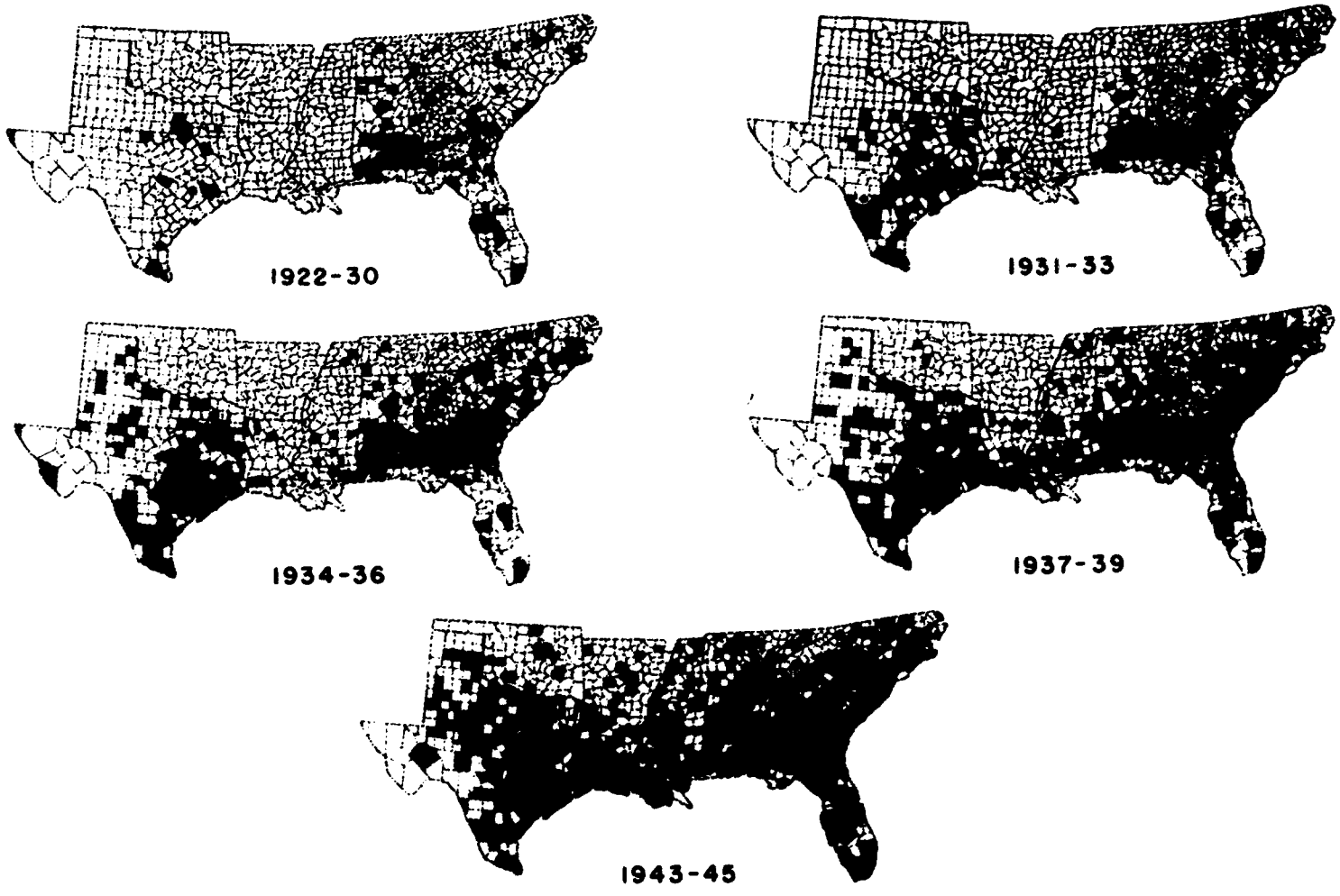
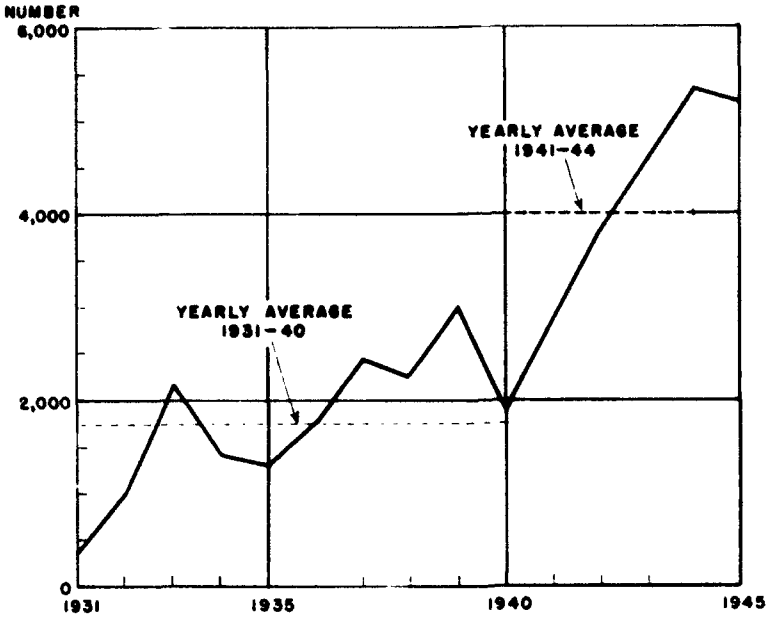


FIGURE 33.—Counties in 11 Southern States reporting cases of endemic typhus fever, 1922–39 and 1943–45. (Reproduced by permission of the American Association for the Advancement of Science.)

CHART 11.—*Total reported cases of murine (fleaborne) typhus in the United States, 1931–45*



Source: Bradley, George H., and Wiley, John S.: The Control of Murine Typhus in the United States. *In* Rickettsial Diseases of Man. Washington: American Association for the Advancement of Science, 1948, pp. 229–240.

TABLE 28.—*Incidence of endemic typhus fever (fleaborne) in the U.S. Army, by area and year, 1942–45*

[Preliminary data based on sample tabulations of individual medical records]

[Rate expressed as number of cases per annum per 1,000 average strength]

Area	1942–45		1942		1943		1944		1945	
	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate
Continental United States	497	0.03	72	0.03	165	0.03	160	0.04	100	0.03
Overseas:										
Europe	5	0.00	----------	0.00	----------	0.00	5	0.00	----------	0.00
Mediterranean [1]	12	.01	----------	0	8	.02	4	.01	----------	0
Middle East	9	.06	----------	0	1	.02	8	.17	----------	0
China-Burma-India	34	.08	----------	0	7	.18	12	.07	15	.07
Southwest Pacific	87	.05	10	.14	39	.21	33	.06	5	0
Central and South Pacific	123	.10	13	.09	65	.22	35	.08	10	.03
North America [2]	1	0	----------	0	----------	0	1	.01	----------	0
Latin America	18	.05	3	.03	1	.01	4	.05	10	.14
Total overseas [3]	290	0.03	26	0.04	122	0.07	102	0.03	40	0.01
Total Army	787	0.03	98	0.03	287	0.04	262	0.03	140	0.02

[1] Includes North Africa.

[2] Includes Alaska and Iceland.

[3] Includes one admission aboard transport in 1943.

Despite the relatively high incidence of endemic typhus, the sporadic and unpredictable occurrence of cases generally prevented clinical studies by Medical Department personnel. A few observations were made, however, which merit record. One of these was an investigation in Jamaica, B.W.I., carried out by Plotz, Woodward, Philip, Bennett, and Evans.[87] Since Jamaica had become a military base for U.S. forces as a result of the lend-lease agreement of 1940, the presence on this island of typhus in any form was a matter of concern to the Medical Department of the Army. The first case of typhus to be recorded in Jamaica was observed by Captain Woodward in December 1941. The patient was a native laborer who complained of fever, headache, and generalized pains on admission to the Army hospital. He was moderately toxic and, aside from conjunctival injection and a few rales at the base of the lungs, there were no other findings. The temperature ranged from 100° to 105° F. for 14 days and fell by lysis. In spite of careful search, no rash was observed. His skin was café au lait in color, and a slight rash may have been missed. The Weil-Felix OX-19 agglutination titer was 1:500 on the 8th day of illness, 1:1,000 on the 9th day, and 1:2,500 on the 12th day. Complement fixation tests indicated that this patient had murine typhus. This case directed attention to the likely presence of murine typhus on the island and led to the investigation. Although 68 cases of the disease were diagnosed, only 33 of these were seen in the hospitals at Kingston. The clinical and laboratory findings in this group were summarized as follows:

> The onset is usually sudden with severe headache, generalized pains, and temperature which is maintained for about 14 days when it falls by rapid lysis. Rash was only seen in 7 cases. In these cases the rash was maculopapular in character. No rash was observed in 26 cases but may have been masked in some instances by the dark skin of the natives. However, some patients, who were carefully observed, showed no rash, and hence the possibility of typhus occurring without an eruption must be considered.
>
> All of the cases had a Weil-Felix (OX-19) agglutination, ranging from 1:500 to 1:5,000; in most of them a rising agglutination titer was observed. Specimens of serum examined for complement fixing antibodies were positive at least late in all cases. In the sera of most patients, complement fixing antibodies were present which reacted with an endemic rickettsial antigen but not with an epidemic rickettsial antigen. In a few cases, convalescent sera had relatively large amounts of complement fixing antibody against an endemic antigen and small amounts against an epidemic antigen.

This study was particularly important in that it proved that endemic typhus was indigenous to Jamaica and had not been introduced by U.S. Army engineer troops in 1941, as had been rumored in some quarters.

A number of workers had voiced suspicion that murine typhus was present in the Philippine Islands. It remained for Woodward, Philip, and

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[87] Plotz, H., Woodward, T. E., Philip, C. B., Bennett, B. L., and Evans, K. L.: Endemic Typhus Fever in Jamaica, B.W.I. Am. J. Pub. Health 33: 812–814, July 1943.

Loranger to establish its endemicity there during the latter part of World War II. The following case was recorded in their report:[88]

On 23 April 1945, an American soldier became suddenly ill with a headache and chill soon followed by fever, general malaise, nausea, and vomiting. At this time and for the 3 previous weeks he was billeted in a large warehouse in San Juan del Monte, a township bordering the outskirts of Manila, Philippine Islands. Rats (*Rattus norvegicus*) had been seen and subsequently trapped in this structure which is situated in close proximity to native dwellings. Social contact in the latter was not denied.

Until 26 April when the patient was admitted to the 5th Field Hospital, the fever, headache, and general malaise continued. These were the presenting symptoms with the physical examination at this time essentially negative. The subsequent 2 weeks' febrile course was of a remittent nature ranging from 99.4° to 104.4° F. On the 15th day the temperature was normal and remained so except for minimal sporadic elevations to 99.4° F. Chills, headache, pains in the chest, abdomen, and lower back were the predominant symptoms during the first week of illness until the sixth day, when irregular, brownish-pink macular lesions appeared on the chest, shoulders, and abdomen. These lesions became more intense and within 24 hours had spread to include the lower extremities and feet at which time the individual macule was fixed on digital pressure. Remnants of the petechial-like lesions were observed until the 15th day of illness when a biopsy of one of the fading macules was performed. Other than faint pigmented spots, there was no evidence of the skin manifestations after the 20th day.

During the early phases of the second week the temperature was high, the patient was moderately toxic with moderate weakness and prostration. The severest phase lasted 4 days until the ninth day when he was symptomatically much improved. Moderate lymphatic glandular enlargement was observed. There were no lesions whatever suggestive of a primary eschar. A slight cough with fleeting pulmonary rales was not remarkable. Delirium and severe central nervous system findings were not observed. By the 13th to 15th day all outward signs of weakness and prostration had disappeared and the patient became steadily stronger.

The treatment, entirely symptomatic, included parenteral physiological saline and glucose solutions, small blood transfusions, supplemental iron, calcium, and vitamins.

Laboratory findings.—Repeated examinations of blood smears for malaria parasites were negative. Urinalyses were within normal limits. Numerous blood counts on 27, 28, and 29 April, 3, 4, 6, and 19 May were normal with the white count ranging from 5,500 to 7,900, and normal differential counts. Red blood cells ranged from 3.8 to 4.5 millions. Stool examinations were noncontributory. Agglutination with the O and H antigens of typhoid and the A and B antigens of paratyphoid fever were negative and two spaced blood cultures showed no growth. Diagnosis was established by the serial examinations of repeated blood specimens as shown in table 29.

Comment.—The clinical features of continued pyrexia for 2 weeks with headaches, absence of marked central nervous system manifestations, and the appearance of a macular body rash on the sixth febrile day (without primary eschar) are strongly suggestive findings of murine typhus fever. A biopsy of one of the late skin lesions demonstrates the capillary changes and perivascular accumulation of cells so frequently observed in rickettsial diseases collectively. The serological findings are unquestionably significant. The patient developed increasing titers of *Proteus* OX–19 agglutinins, as shown by tests performed employing suitable control serums. Agglutinins for *Proteus* OX–K did not appear. More significantly, complement fixation on serial specimens of serums using

[88] Woodward, T. E., Philip, C. B., and Loranger, G. L.: Endemic Typhus in Manila, Philippine Islands; Report of Cases and the Identification of Murine Rickettsial Agent in Domestic Rats by Complement Fixation. J. Infect. Dis. 78: 167–172, March-April 1946.

purified murine (yolk-sac culture) rickettsiae as antigen clearly demonstrated antibodies of sufficient diagnostic titer (table 29). The low titer of 1:6 using an epidemic typhus antigen is within the normal range of cross fixation frequently observed when these two closely related antigens are employed to detect antibodies in the serum of the typhus patient. Studies by Plotz and his collaborators, based on the use of purified antigens, have clarified the serological patterns in epidemic and murine typhus fevers.

TABLE 29.—*Serological studies on an American soldier with murine typhus*

Day of illness	Proteus OX-19	Agglutination OX-K	Complement fixation	
			Murine	Epidemic
7th	0	0		
16th	1:2,560			
19th	1:2,560	0	1:384	1:6
24th	1:2,560	0	1:96	1:6
31st	1:1,280	0	1:96	0

Source: Woodward, T. E., Philip, C. B., and Loranger, G. L.: Endemic Typhus in Manila, Philippine Islands, Report of Cases and Identification of the Murine Rickettsial Agent in Domestic Rats by Complement Fixation. J. Infect. Dis. 78: 167-172, March-April 1946.

Woodward and his coworkers noted two other cases which occurred in Manila, and another which originated on Mindanao. In addition, they found that 18 percent of rats trapped in Manila gave evidence of endemic typhus infection as detected by complement fixation tests with purified rickettsial antigens.

Woodward also observed murine typhus in Morocco.[89] There, Dr. Georges Blanc of the Pasteur Institute undertook to determine the efficacy of a living murine typhus vaccine in human volunteers. This study gave Woodward an opportunity to follow closely the incubation period and clinical course of endemic typhus. Although no clinical report was issued, the pertinent observations made at that time were incorporated in his later description of the disease.[90]

Murine typhus was encountered by other U.S. Army medical officers, but no series of cases was reported as a clinical study. Scoville, Bennett, Wertman, and Gauld,[91] for example, obtained data on 15 cases which occurred in Nashville, Tenn., during September 1944, focusing upon serological aspects of the disease. Similarly, Plotz and Wertman[92] described 12 cases

[89] Letter, Capt. Theodore E. Woodward, MC, to Director, U.S.A. Typhus Commission, 14 Dec. 1943, subject: Report of Human Typhus Fever Vaccine Experiment.

[90] Woodward, Theodore E.: Endemic (Murine) Typhus Fever: Symptomatology. *In* Rickettsial Diseases of Man. Washington: American Association for the Advancement of Science, 1948, pp. 134-138.

[91] Scoville, A. J., Jr., Bennett, B. L., Wertman, K., and Gauld, R. L.: The Serological Pattern in Typhus Fever. II. Murine. Am. J. Hyg. 47: 166-176, March 1948.

[92] Plotz, H., and Wertman, K.: Modification of Serological Response to Infection With Murine Typhus by Previous Immunization With Epidemic Typhus Vaccine. Proc. Soc. Exper. Biol. & Med. 59: 248-251, June 1945.

of murine typhus contracted after immunization with epidemic typhus vaccine (table 30), again with the emphasis on the serological findings, which are to be discussed.

TABLE 30.—*Serological results found in individuals who were previously immunized with epidemic typhus vaccine and who subsequently contracted murine typhus*

Case	Day of disease	Typhus vaccine	Serological results						Date of onset	Where infected	Severity of infection
			Complement fixation		Rickettsial agglutination		Weil-Felix [1]				
			Epidemic	Murine	Epidemic	Murine	OX-19	OX-2			
A	59	November 1943.	1,280	320	80	640	80	80	1 Jan. 1944	Waycross, Ga.	Moderately severe.
	90		1,280	320	160	1,280	0	0			
S	21	September 1942.	640	320	80	1,280	2,560	0	20 Nov. 1944	Fort Benning, Ga.	Do.
	42		320	320	80	640	640	0			
	58		160	160	80	320	640	0			
Si	27	27 May 1944.	A/C	A/C	2,560	10,240	160	40	19 July 1944	Louisiana	Severe.
	159		320	160	320	2,560	160	40			
P	22	September 1944.	1,280	640	320	640	160	0	17 Dec. 1944	Camp Gordon, Ga.	Do.
	50		1,280	640	320	320	0	0			
B	18	November 1944.	160	40	5,120	10,240	640	0	23 Nov. 1944	Camp Shanks, N.Y.	Moderately severe.
	21		160	160	5,120	10,240	320	0			
	26		160	160	5,120	10,240	0	0			
	31		160	160	5,120	10,240	0	0			
Be	18	August 1944.	640	160	5,120	10,240	1,280	0	25 Nov. 1944	Birmingham, Ala.	Do.
	70		320	160	160	1,280	160	0			
Ben	38	October 1944.	80	80	1,280	5,120	640	40	24 Oct. 1944	Tampa, Fla.	Mild.
K	30	September 1944.	160	80	5,120	10,240	80	0	18 Sept. 1944.	Camp Miles Standish, Mass.	Do.
Ba	15	December 1944.	80	10	1,280	5,120	640	320	15 Dec. 1944	Robins Field, Ga.	Do.
F	44	January 1944.	80	80	640	5,120	640	0	2 Jan. 1945	Austin, Tex.	Moderately severe.
	55		80	40	160	2,560	1,280	40			
T	45	July 1944.	1,280	640	1,280	5,120	1,280	160	14 Jan. 1945	San Antonio, Tex.	Mild.
Com	14	August 1943. Recall dose May 1944.	320	320	160	640	160	0	12 July 1944	Hunter Field, Ga.	Do.
	23		A/C	A/C	1,280	2,560	160	40			
	24		320	320	1,280	5,120	80	40			
	30		320	160	320	2,560	40	0			
	37		320	160	320	2,560	0	0			

[1] Cases S, P, B, Ba, and T showed a rise in OX-19 titer when serum specimens were examined during the febrile period and early convalescence while the other cases showed high titers. These examinations were made in the hospitals where the patients were treated. It should be observed that the specimens which were available for this study were frequently obtained late in convalescence.

Source: Plotz, H., and Wertman, K.: Modification of Serological Response to Infection With Murine Typhus by Previous Immunization With Epidemic Typhus Vaccine. Proc. Soc. Exper. Biol. & Med. 59: 248–251, June 1945.

Zarafonetis [93] reported the epidemiological, clinical, and laboratory findings in two U.S. Army enlisted men who were stationed in Dakar, French

[93] Letter, Capt. Chris Zarafonetis, MC, U.S.A. Typhus Commission, to Chief Surgeon, U.S. Army Forces in the Middle East, through Brig. Gen. Leon A. Fox, Field Director, U.S.A. Typhus Commission, 10 Aug. 1944, subject: Report of Typhus Situation in Dakar.

West Africa, at the time of their illness. Brief summaries of their case histories follow.

A 27-year-old private (case 1) was admitted on 5 July 1944 with the diagnosis of acute tonsillitis. He had a 1-day history of sore throat and difficulty in swallowing, and there were associated complaints of joint pains and aching. Physical examination was essentially negative except for evidence of tonsillar involvement. Temperature at that time was 99.6° F. On the following day, the patient complained of a headache which was not relieved by aspirin and other analgesics and which persisted for several days thereafter. On 9 July the patient experienced a chill and complained of generalized aching. His temperature reached 102.4° F., which was the maximum attained during his hospitalization. From 9 July until 24 July, he continued to run a low-grade fever. At no time was there a rash evident. Serum taken on 12 July was tested at the Pasteur Institute at Dakar and found to agglutinate *Proteus* OX–19 in dilution of 1:200. Serum was tested again on 18 July and this time agglutinated OX–19 to a titer of 1:1,000. On the basis of the laboratory findings a diagnosis of typhus was made.

The second case was that of a 23-year-old T/5 (case 2) who was admitted on 18 July with complaint of severe headache and pain in the chest for 24 hours prior to admission. His physical examination at that time was essentially negative except for an admission temperature of 101.6° F. On 25 July, the 10th day of disease, a fine macular rash appeared over the chest and arms.

The rash had practically disappeared by 27 July. Fever had been present continuously for 15 days but was falling toward normal on 29 July. His course had been relatively mild for typhus.

These two patients were believed to have had murine typhus principally on the basis of epidemiological evidence. Durieux and other French workers had concluded from extensive studies of typhus in French West Africa that the louseborne form of this disease did not exist there. However, some 200 cases of relatively mild typhus had been diagnosed during the preceding decade, with only 1 death recorded. The strains of rickettsiae that had been isolated from some of these cases were all identified as *R. mooseri*. At the time the American soldiers contracted their illness, two other cases, both unrelated, occurred in the native population. Because of an outbreak of plague in Dakar, both soldiers had remained within their military establishments for over a month prior to the onset of their illness. An intensive antirat campaign was underway, and many rats were known to have been present in the areas where these soldiers contracted their typhus. Both patients were aware of frequent fleabites prior to their illness but recalled no contact with lice.

On this evidence, Zarafonetis concluded that both patients had murine typhus and were of particular interest as instances in which epidemic typhus vaccination had been followed by murine typhus infection.[94] The results of serological studies in these two cases are presented in table 31.

The foregoing reports, some of which were fragmentary, contained the principal clinical references made by U.S. Army personnel to murine typhus during World War II. To be sure, many individual cases were observed in

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[94] See footnote 35 (3), p. 183.

Hawaii [95] and other areas to which U.S. Army troops were sent,[96] but these were not the subject of clinical reports.

TABLE 31.—*Serological findings in two cases of probable murine typhus fever occurring in vaccinated individuals at Dakar, French West Africa*

Case	Amount of Cox-type vaccine	Last vaccinated	Onset of illness	Days of fever	Days of serum specimen from onset	Serological findings			
						Weil-Felix		Complement fixation	
						OX-19 [1]	OX-2 [1]	Epidemic	Murine
1		14 June 1944	5 July 1944	24	9	1:200 [2]	Not done	Not done	Not done.
					15	1:1,000 [2]	do	do	Do.
					22	1:1,280 P 1:2,560	1:40 P 1:80	1:512 [3]	1:256 (a)
					25	1:1,280 P 1:2,560	Negative	1:512	1:256
					30	1:1,280 P 1:2,560	do	1:256 [3]	1:256 (a)
					47	1:320	do	1:256	1:128
2	6	2 May 1944	17 July 1944	15	12	1:320 P 1:640	1:40 P 1:80	1:512 [3]	1:256 (b)
					13	1:640 P 1:1,280	Negative	1:512	1:256
					17	1:640 P 1:1,280	do	1:1,024 [3]	1:256 (b)
					34	1:640 P 1:320	do	1:512	1:256
					71	1:40 P 1:80	do	1:256 [3]	1:64 (b)

[1] Weil-Felix agglutination titers of less than 1:40 are arbitrarily considered negative. P=Partial agglutination. Tests with OX-K suspensions were negative.

[2] Performed at Pasteur Institute, French West Africa.

[3] Tests on these specimens at the Army Medical Department Professional Service Schools, Army Medical Center, Washington, D.C., gave titers of 1:640 with epidemic antigen, while murine antigen tests yielded titers of 1:320 for the specimens followed by (a) and 1:640 for those followed by (b).

Source: Modified from Zarafonetis, C. J. D., Ecke, R. S., Yeomans, A., Murray, E. S., and Snyder, J. C.: Serologic Studies in Typhus-Vaccinated Individuals; Weil-Felix and Complement-Fixation Findings in Epidemic Typhus Fever Occurring in the Vaccinated. J. Immunol. 53: 15–30, May 1946.

LABORATORY AIDS IN DIAGNOSIS

The same laboratory procedures that were employed as diagnostic aids in epidemic typhus fever were also applied to murine typhus fever. The Weil-Felix *Proteus* OX–19 agglutination test and complement fixation and rickettsial agglutination tests with purified rickettsial antigens have the same degree of specificity and diagnostic values here as they have for epidemic typhus fever. Table 32 gives the results of each of these tests on sera from a nonvaccinated individual with murine typhus. The reader is referred to the laboratory section under epidemic typhus for detailed discussion of these and other diagnostic procedures which may be of value in murine typhus, such as the mouse-toxin neutralization test and strain isolation.

It will be recalled that while the complement fixation test with purified rickettsial antigens was specific for the homologous form of typhus, this test lost its high degree of specificity in patients with epidemic typhus fever who had been previously immunized with epidemic typhus vaccine of the

[95] Essential Technical Medical Data, United States Army Forces, Pacific Ocean Areas, for July 1944.

[96] See footnote 4, p. 144.

Cox type,[97] and the theory advanced by Zarafonetis to explain this finding has been discussed (p. 186). On inspection of table 31 it will be seen that a similar loss of specificity was found in tests on sera from murine typhus patients who had been vaccinated against epidemic typhus fever. Plotz and Wertman[98] independently made the same observations. They had performed tests on sera from 147 cases of murine typhus in soldiers stationed in the United States. Of these, 135 had the typical serological response for murine typhus comparable to the pattern shown in table 32, but in 12 cases an unusual response was noted, as can be seen in table 30. These workers investigated these 12 patients with some care in an attempt to determine the factors responsible for the atypical serological findings.

TABLE 32.—*Serological results in a nonvaccinated individual infected with murine typhus fever (case 1)—strain isolated*

Day of disease	Serological results						
	Weil-Felix			Complement fixation		Rickettsial agglutination	
	OX-19	OX-2	OX-K	Epidemic	Murine	Epidemic	Murine
5th	0	0	0	0	0	0	0
7th	1:80	0	0	0	0	0	1:160
9th	1:640	1:160	1:40	0	0	1:80	1:1,280
11th	1:640	1:160	1:80	0	0	1:160	1:2,560
13th	1:640	1:160	1:40	0	0	1:320	1:5,120
14th	1:640	1:80	1:40	0	0	1:320	1:5,120
16th	1:640	1:80	0	0	0	1:320	1:5,120
18th	1:320	0	0	0	1:80	1:320	1:5,120
20th	1:160	0	0	0	1:160	1:640	1:10,240
22d	1:160	0	0	0	1:320	1:640	1:10,240
31st	1:160	0	0	0	1:320	1:320	1:5,120
75th	0	0	0	1:40	1:320	1:40	1:1,280
123d	0	0	0	1:40	1:320	0	1:160

Source: Plotz, H., and Wertman, K.: Modification of Serological Response to Infection With Murine Typhus by Previous Immunization With Epidemic Typhus Vaccine. Proc. Soc. Exper. Biol. & Med. 59: 248–251, June 1945.

It was found that all of these patients had received typhus vaccine some time or other within the preceding 2 years. The vaccine used consisted of formalinized epidemic rickettsiae with no murine rickettsiae whatsoever. All cases occurred in regions of the United States where murine typhus alone is known to exist and in some instances other cases of murine typhus were present in the same camp at the time these cases were admitted to the hospital. The clinical diagnosis of murine typhus seems to have been well substantiated. All cases developed a typical rash. A rise in OX–19 titers occurred in the late febrile period and early convalescence in 6 cases, while most of the others showed high titers. The febrile period varied from 8 to 23 days with an average of about 14 days. Unfortunately, no attempt was made to isolate the agents.

97 See footnote 35 (3), p. 183.
98 See footnote 92, p. 210.

These investigators note further that, while many of the specimens in these 12 vaccinated cases showed higher complement fixation titers to epidemic than to murine antigen, there was considerable cross-fixation and a number of specimens were equally responsive to both antigens (table 30). They contrast this with the nonvaccinated patients infected with epidemic typhus, in whom there are high titers to epidemic antigens with, as a rule, no considerable cross-fixation. Again, in nonvaccinated patients with murine typhus, the complement fixation titer is higher with homologous than with heterologous antigen, and there is little crossing (table 32). On the other hand, rickettsial agglutination, in the 12 nonvaccinated cases, usually showed a higher titer to the murine antigen, but in many instances there was only a twofold difference in titer, and here again cross-agglutination is marked. The same type of antibody response occurred whether the typhus vaccine had been given 2 years or 1 week before the attack of murine typhus and was not seen in patients vaccinated against typhus who subsequently became infected with atypical pneumonia, measles, infectious hepatitis, smallpox, meningitis, or other viral, bacterial, or protozoal infections. As regards symptoms and clinical course, they note, the previous vaccination against epidemic typhus had no apparent effect upon the severity of the subsequent attack of murine typhus.

Thus, the rickettsial agglutination test appeared to offer the most reliable means by which one might make the serological diagnosis of murine typhus in a patient who had previously been immunized with the Cox type of epidemic typhus vaccine.

Part IV. Summary

EPIDEMIC TYPHUS

Our knowledge of typhus fever at the beginning of the war was so incomplete, and during the war was so greatly expanded, that it seems appropriate to sketch here the composite picture of epidemic typhus that now emerged.

Clinical picture.—The incubation period of louseborne typhus fever varies from 7 to 20 days, with the usual onset about 10 to 12 days after infection occurs. A prodromal stage of ill-defined malaise probably exists for a few days, but is of no diagnostic value. In the majority of adult patients, the clinical onset is abrupt with malaise, chills or chilly sensations, followed by severe headache and fever. There is anorexia, and sometimes vomiting. The temperature rises rapidly during the first day or two to 104° F., or higher, where it remains throughout the greater part of the acute illness. The pulse rate usually exceeds 100 beats per minute and remains full at least throughout the first days of illness. Severe aches and pains appear early, and the thigh and calf muscles are sensitive to pressure. An

early symptom is a roaring sound in the ears, which may be followed by temporary deafness. Dyspnea and cough appear by the second or third day. The tongue and mouth become dry and fissured, and thirst is a common symptom. The patient is tense and anxious from the beginning, but mental disturbances do not usually appear until about the end of the first week. These may be stupor or a period of excitement, even of delirium.

There are no diagnostic features prior to the characteristic eruption, appearing usually between the fifth and seventh day of disease. Initially, it consists of faint rose-colored spots, 2 to 6 mm. in diameter, round to irregular in shape. The lesions first appear over the upper anterior chest wall, in the axillae and inner surfaces of the upper arms, on the abdomen, lower back, and buttocks. The rash usually develops rapidly and extends in a few hours to cover the back, the lower arms and dorsal aspects of the hands, and the legs to the knees. The face and scalp are spared; only rarely does the eruption involve the palms and soles (fig. 34). The characteristic lesion is macular at first, but may become papular after a few hours. At the beginning, the lesions will fade on pressure, but they usually become fixed within 24 hours. Also, as the disease progresses, the lesions increase in number and size and may become confluent. Along with the appearance of the rash, the conjunctivae become injected and the eyelids appear puffed. The face may take on a dusky, cyanotic hue. Typically, the eruption fades rapidly at the time of defervescence.

By the end of the first week, the patient enters the critical stage. The fever continues unabated, the delirium and cough are intensified. The heart rate is rapid and hypotension develops. The patient may be incontinent of urine and feces and may be all but helpless. In the absence of complications, there may be gradual improvement as the fever begins to fall some 2 weeks or more after its onset. Some patients undergo a crisis with return of the temperature to normal in 24 hours, while in others the decline may be gradual over a period of 2 or 3 days. As the fever disappears, the headache vanishes, the mind clears, and the appetite returns. Recovery of strength and nutrition is fairly rapid, but deafness and tinnitus may persist for several weeks.

The clinical picture can vary widely, depending on what organs are predominantly involved or on complications. Pathological studies have shown that the rickettsiae localize first in endothelial cells of the intima and then enter large mononuclear cells which collect about blood vessels. Proliferation of vascular endothelium and of mononuclear cells around blood vessels results in nodular accumulations. This focal, endothelial, proliferative, and infiltrative response to the infection occurs in the skin, brain, heart, skeletal muscles, spleen, adrenals, and other organs in varying degree. Clinically, the characteristic rash and signs referable to the central nervous system reflect the underlying lesions. The myocardium is also commonly affected, while the lungs may show a rickettsial pneumonitis.

The leukocyte count is frequently reduced during the first week, with neutropenia and a relative lymphocytosis. Eosinophils are absent or reduced during the febrile course. Mild normochromic anemia not uncommonly develops, but there is a return to normal values during convalescence. Albuminuria is uniformly present during the period of fever. Granular casts usually appear in large numbers in patients with azotemia. Elevation of the blood urea nitrogen is often observed during the second week of illness, especially in severely ill patients. The total serum proteins may be normal or slightly reduced, but reversal of the albumin-globulin ratio is commonly noted. This is due to an increase in serum globulin, the values for which usually range from 4 to 5 mg. percent. Reduction in the serum chlorides is also common. Apparently, the chlorides are not lost through excretion during the disease, since the values spontaneously return to normal after defervescence.

Diagnosis.—During an epidemic of typhus fever, the diagnosis may be suspected before the appearance of the rash. A history of abrupt onset with chills, fever, severe headache, louse infestation, or contact with lice or with typhus patients leaves little doubt as to the nature of the illness. Certain other coexistent diseases may, however, complicate early diagnosis. Smallpox, louseborne relapsing fever, typhoid, and meningococcal meningitis may all be confused with early typhus. Once the characteristic rash has appeared there is usually little difficulty in making a clinical diagnosis, although meningococcemia, measles, and relapsing fever with exanthem must also be considered. Murine typhus is not clinically distinguishable from louseborne typhus in the individual case. Differentiation between these two forms of typhus fever, as well as establishment of the final diagnosis, is dependent upon certain laboratory studies. The diagnosis may be made by isolating the micro-organism from the blood of the patient and identifying it through biological and other tests. More practical, however, being less expensive and time consuming, are the serological tests, which include complement fixation with purified rickettsial antigens, rickettsial agglutination, and Weil-Felix *Proteus* OX–19 agglutination. These should be performed on two or more serum specimens obtained from the patient during the acute illness and convalescence in order to detect a significant change in antibody titer. Sera from patients with louseborne typhus fever, in complement fixation tests, yield higher titers with epidemic typhus antigen than with murine antigen. The same relationship obtains in rickettsial agglutination tests. With respect to the OX–19 test, a significant change in titer may be observed but is relatively nonspecific, since it occurs in murine typhus and Rocky Mountain spotted fever as well as in epidemic typhus fever. Usually, all three of these tests reveal diagnostic (fourfold or more) changes in titer with their respective antigens. Rarely, however, there may be a dissociation of response, and one of the tests may give completely negative results throughout. Sera from patients who have contracted epidemic typhus fever after vaccination against

FIGURE 31. Typhus fever patient on U.S.A. Typhus Commission Ward, Fever Hospital, Cairo, Egypt. A, On 18 April 1918, the 10th day of disease, the eruption is clearly evident on the chest and upper arms. B, Same day, seen on the back.

FIG. 88.31. Continued. C, Same day, although sparse, the eruption was also present on the palms. D, On 2 May, 24th day of disease, the rash has now disappeared and the patient is convalescing. Note loss of weight.

it exhibit much more cross-reaction in the complement fixation tests than do sera from unvaccinated patients, but the rickettsial agglutination test appears to retain specificity in vaccinated as well as in nonvaccinated cases.

Natural course.—In the untreated case (that is, the unvaccinated patient given no specific therapy), typhus fever runs its course in 14 to 20 days unless terminated by death. The mortality varies in different epidemics and is also greatly influenced by age. An overall death rate of 20 to 30 percent was reached in Egypt and at Naples during World War II in patients 18 to 50 years old. At the Dachau Concentration Camp, however, the typhus death rate was only 9.1 percent. In past epidemics, the fatality rate has been as high as 70 percent. The disease is relatively mild in children, but it tends to be severe with a high mortality in old people.

Deaths are rare in the first week of illness. In severely ill untreated patients, evidence of increasing involvement of the central nervous system often appears during the second week of disease. They may become deeply stuporous, comatose, and die. Convulsions presage a fatal outcome. Other patients develop signs of renal insufficiency, and still others present the picture of peripheral vascular collapse during the second week. There is a striking correlation between clinical severity and the development of azotemia with elevated blood urea nitrogen and creatinine levels. These changes appear to be caused primarily by extrarenal factors, such as greatly increased protein breakdown, dehydration, and hypotension, rather than by a true diffuse renal lesion. Azotemia was detected in every fatal case of the Cairo series, although not every patient who exhibits this change will die. Survivors showed no evidence of renal impairment when tested several months after the acute episode.

The appearance of peripheral circulatory failure is usually indicative of impending death. The extremities become cold and cyanotic, the blood pressure drops to low levels, and the pulse becomes rapid. The basis for this peripheral vascular failure is unknown, but extensive involvement of the capillaries, injury to the vasomotor centers of the brain, and severe myocarditis are probably important contributing factors. Electrocardiographic findings in typhus fever are nonspecific and consist of low voltage, inverted T waves, depression of ST segments, and an increase in PR interval.

The most important complications are bacterial pneumonia, multiple skin abscesses, and parotitis. Although gangrenous involvement of the extremities has been associated with a number of typhus epidemics, it was rarely observed in World War II outbreaks, except at Belsen.

Immunity and relapse.—Immunity is good in untreated subjects who recover from epidemic typhus fever. Delayed relapses do occur, however, and constitute Brill's disease. Relapses are common in patients who receive rickettsiostatic therapy during the first few days of illness, but uncommon if treatment is initiated after the eruption has appeared.

Therapy.—During World War II, PABA was found to have antirickettsial properties and was effective in the treatment of epidemic typhus fever in patients who had as well as in those who had not been vaccinated. Thoroughly studied, it was brought to the position of a safe and promising drug for clinical use.

Prophylaxis.—Effective protection of the troops was accomplished by the use of a potent vaccine and its production in adequate quantities, and by improved methods of louse control.

ENDEMIC (MURINE) TYPHUS

Although the studies on murine typhus during World War II were relatively limited in comparison with those undertaken in connection with epidemic typhus fever and scrub typhus, there was accumulated nevertheless sufficient information upon which to base the following summary description of the disease.

Clinical picture.—The incubation period from actual exposure to the onset of acute illness ranges from 8 to 16 days. Woodward noted that headache, backache, and arthralgia are frequently experienced during the fourth to sixth day after exposure. For a day or so prior to the onset of illness, prodromal symptoms such as nausea and general malaise are common. The disease then begins with chills or chilly sensations, headache, and fever. Nausea and vomiting frequently occur during this early period. Generalized aches and muscular weakness may be pronounced.

The clinical features of murine typhus resemble those of epidemic typhus except that, in the average case the disease is less severe than in the majority of cases of epidemic typhus. In endemic typhus, the patient's temperature increases in stepwise fashion for 3 or 4 days until it reaches its maximum level, and then usually ranges between 103° and 104° F. until defervescence occurs. The total febrile course averages 12 days, but may be a few days longer or shorter. Defervescence is by lysis over 2 or 3 days. A rash is observed in about 80 percent of cases, typically appearing on the fifth day of illness, but it may be seen several days earlier or later. When present, its character and distribution are similar to that in epidemic typhus. Occurring in all degrees of intensity, it usually persists for about 5 days, but may be ephemeral or may remain evident for 10 days.

In addition to intense headache, which is usually frontal, the average patient with murine typhus exhibits mild stupor, prostration, and lethargy. Transient partial deafness occurs at times. As in epidemic typhus, some involvement of the respiratory tract is common. A dry, hacking cough develops, usually in the second week, and crackling rales may be heard in the base of the lungs. These are believed to be manifestations of interstitial pneumonitis of rickettsial origin.

The pulse rate is increased and is usually regular. Minor electrocardiographic changes of nonspecific nature may be detected for a brief period. Persistent hypotension is not uncommon, especially during the second week of acute illness, and is attributed to a combination of factors including extensive vasculitis of the capillaries of the skin and other organs and involvement of the brain with injury to vasomotor centers. Clinical signs of myocardial failure are usually lacking, but this does not rule out myocarditis, which has been found in fatal cases of epidemic typhus fever.

There are no characteristic changes in the formed blood elements. Moderate albuminuria is not uncommon. Azotemia may develop in severe cases and is believed to be largely due to extrarenal factors.

Diagnosis.—An illness characterized by an abrupt onset with headache, chills or chilly sensations, fever, malaise, prostration, nonproductive cough, and later the appearance of a rash should suggest typhus fever among the diagnostic possibilities. Epidemiological considerations and characteristics of the rash may aid in arriving at a tentative clinical diagnosis, but final differentiation rests upon the use of appropriate laboratory tests. These include complement fixation with purified rickettsial antigens, Weil-Felix *Proteus* OX–19 agglutination, rickettsial agglutination, and isolation of the strain by animal inoculation. The last is not practical for routine use, but the serological tests are adequate and more practical. They should be performed on two or more sera obtained from the patient during the acute illness and convalescence to show a diagnostic change in antibody titer. In endemic typhus, titers will be considerably higher with endemic than with epidemic antigen in the complement fixation test. The same relationship obtains in rickettsial agglutination. A significant rise in OX–19 agglutination titer may be helpful, but it does not differentiate between endemic typhus, epidemic typhus, and Rocky Mountain spotted fever. Sera from patients who have previously received epidemic typhus vaccine, and later contracted murine typhus, exhibit much more cross-reaction in complement fixation tests than do sera from nonvaccinated persons. The complement fixation test, therefore, does not differentiate the two forms of typhus in these patients, but the rickettsial agglutination test, according to available evidence, retains specificity in such cases.

Natural course.—The usual course in adults is uncomplicated, with subsidence of fever toward the end of the second week, followed by an uneventful convalescence. The disease is readily tolerated by children, but less well by elderly persons. The mortality is 1 to 2 percent. Complications are infrequent and usually consist of secondary infections which give rise to parotitis, otitis media, or bacterial pneumonia.

Immunity.—After an attack of murine typhus, immunity is apparently of long duration. Recrudescence, in a manner analogous to Brill's disease, has not been reported.

Therapy.—Treatment is the same as for epidemic typhus fever. Smith [99] and civilian workers [100] independently demonstrated the beneficial effect of large doses of PABA in the management of murine typhus.

Prophylaxis.—Control measures are directed at reducing the rat populations that serve as the reservoir of the disease and the rat ectoparasites that serve as the vectors. Rat control measures include general sanitation, rat poisoning, and ratproofing of buildings. The principal method of ectoparasite control is by DDT dusting of ratruns and harborages.[101]

Prophylactic vaccination, although possible, is not usually practical in view of the sporadic occurrence of cases.

EPILOGUE

The preventive, clinical, and laboratory events concerned with the typhus fevers during World War II represent a brilliant chapter in the history of medicine. Many contributions were outside the scope of this review and are detailed elsewhere.[102] No historical summary of typhus would be complete, however, without acknowledgment of the keen stimulation and wise guidance provided by Brig. Gen. Stanhope Bayne-Jones and Brig. Gen. Leon A. Fox, Director and Field Director, respectively, of the United States of America Typhus Commission. The U.S. Army Medical Department can be justly proud of the contributions made by its members under the leadership of these men.

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[99] Smith, P. K.: The Use of Para-Aminobenzoic Acid in Endemic (Murine) Typhus Fever. J.A.M.A. 131: 1114-1117. 3 Aug. 1946.

[100] Levy, M. D., and Arnold, W. T.: Para-Aminobenzoic Acid in the Treatment of Endemic Typhus Fever. Texas State J. Med. 42: 314-316, September 1946.

[101] See footnote 85, p. 205.

[102] See footnote 4, p. 144.

CHAPTER VIII

Rheumatic Fever

Lowell A. Rantz, M.D.

Rheumatic fever has been a problem to the U.S. Army in all of its wars for which historical data are available, although it attracted little attention before World War II. Enteric infection and malaria in earlier wars, and influenza and its complications in World War I, overshadowed all other acute diseases. Inadequate diagnosis also prevented the recognition of the military importance of this disorder.

The recorded experience of the U.S. Army in the American Civil War[1] reveals that acute rheumatism occurred with remarkable frequency. In 5.2 years, 146,000 cases were reported among white troops at a rate of 61 per 1,000 per annum. Certainly, not all of these were acute rheumatic fever, but examination of the case records that have been preserved in the history of that war indicates that a substantial number of them was certainly this disease. This impression is confirmed by 642 deaths caused by rheumatism, endocarditis, and pericarditis. Furthermore, the disease occurred principally in the winter among fresh levies of troops, an epidemiological pattern which resembles that of rheumatic fever during World War II. In retrospect, it is impossible to define the magnitude of the problem of rheumatic fever in the Civil War, but it must have been great.

The situation during World War I was similar.[2] There were 24,770 admissions for acute articular rheumatism reported, but the significance of this disease was apparently overlooked even though it was occurring at the rate of 6.00 per 1,000 per annum. The fact that many of these cases were rheumatic fever was not appreciated, and this disease is not mentioned by name in the official history of the Medical Department in World War I. The disease occurred with greatest frequency in the same areas as it did during World War II but at substantially higher rates.

In spite of this background and of the great advances that had been made in the period between the wars in knowledge of the pathogenesis and natural history of the disease, the U.S. Army Medical Department was poorly equipped to cope with the problem of rheumatic fever in the first years of World War II. This was largely the result of several well-defined factors. The first, and most important, was the failure of the Medical Department to realize the importance of rheumatic fever as a military problem. Rheumatic

[1] Medical and Surgical History of the War of the Rebellion. Medical History. Washington: Government Printing Office, 1870, pt. I, vol. I, pp. 637-639.

[2] The Medical Department of the United States Army in the World War. Washington: Government Printing Office, 1925, vol. XV, pt. 2, p. 86.

fever was not required to be reported by all facilities on the weekly statistical summary until December 1941 [3] and was often incorrectly diagnosed during the following 2½ years.

Of equal importance was the failure to appreciate the intimate relationship between infection by group A hemolytic streptococci and rheumatic fever. Medical officers in the field were not trained to distinguish streptococcal from nonbacterial respiratory disease, so that the hemolytic streptococcus was only recognized during the period 1940–43 as a common cause of illness in those few camps where scarlet fever was occurring frequently. The importance of the case without a rash was not realized. Lastly, the Army and its consultants had not familiarized themselves with available civilian and military data which would have made it possible to predict with considerable accuracy those geographic areas in which outbreaks of hemolytic streptococcal infection and rheumatic fever might be expected.

Little information is available as to the situation during the prewar expansion of the Armed Forces. During 1941, outbreaks of scarlet fever followed by rheumatic fever occurred at Chanute Field, Ill., Scott Field, Belleville, Ill., and Fort Knox, Ky. The incidence of these diseases elsewhere in the Army during 1941 was low. Drs. James D. Trask, Francis F. Schwenkter, and M. Henry Dawson, of the Commission on Hemolytic Streptococcal Infections, Army Epidemiological Board (Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army), visited each of these camps in November 1941. They noted that medical officers did not recognize the association of scarlet fever and streptococcal disease occurring without a rash nor did they connect either of them with rheumatic fever.[4]

The available records do not reveal that streptococcal disease was viewed with alarm during the period 1941–42, although the incidence of scarlet fever, in the total Army, during those years was comparable to that in 1943–44 when interest in infection by these organisms was very great. This was the result of the mildness of the acute streptococcal disease and of the failure to report accurately the occurrence of rheumatic fever prior to 1943.

The first detailed information in regard to the problem of rheumatic fever was obtained early in February 1943 when a survey of the continuing scarlet fever epidemic at Fort Francis E. Warren, Wyo., revealed that more than 100 patients with this disease had been hospitalized but neither correctly diagnosed nor reported to The Surgeon General.[5] Subsequently, the rapid increase in size of installations in areas of high incidence of this dis-

[3] Circular Letter No. 123, Office of the Surgeon General, U.S. Army, 16 Dec. 1941, subject: Medical Department Form 86ab, Statistical Report (first section).

[4] Report, M. Henry Dawson, M.D., Director, Commission on Hemolytic Streptococcal Infections, Army Epidemiological Board, 24 Nov. 1941, subject: Report on Reconnaissance Trip to the Fifth and Sixth Corps Areas by Dr. James D. Trask, Dr. Francis F. Schwenkter, and Dr. M. Henry Dawson, Members of the Commission on Hemolytic Streptococcal Infections, November 11–19, 1941.

[5] Report, Lowell A. Rantz, M.D., Member, Commission on Hemolytic Streptococcal Infections, Army Epidemiological Board, to Col. S. Bayne-Jones, Office of the Surgeon General, 23 Feb. 1943, subject: Report of Epidemic of Scarlet Fever and Septic Sore Throat, at Fort Francis E. Warren.

ease in Colorado and Utah was associated with epidemics of streptococcal infection and rheumatic fever. Additional surveys were made which again delineated the deficiencies in background and information on the part of medical officers in regard to streptococcal respiratory disease and its complications, although no control measures were recommended.[6]

During 1943, 6,710 admissions for rheumatic fever were reported from the Army in the United States. According to summaries of the statistical health reports, about 74 percent of these occurred in the Seventh and Ninth Service Commands. About 43 percent of all cases occurred in the States of Colorado, Utah, Idaho, Montana, and Wyoming. This large number of cases of a serious disease requiring prolonged hospital care and resulting in many separations from service attracted a very considerable interest in the offices of The Surgeon General of the Army and of the Air Surgeon. Three programs designed to acquire new knowledge about hemolytic streptococcal disease with special reference to its relationship to rheumatic fever and to control methods were instituted toward the end of 1943. All were conducted in the field with the active assistance and cooperation of many command and medical officers.

One of these programs was under the auspices of the Commission on Hemolytic Streptococcal Infections. Its purpose was the careful investigation of a large number of cases of hemolytic streptococcal respiratory infection for the purpose of defining the natural history, bacteriology, and immunology of these disorders. Associated with this group was the Commission on Air-Borne Infections, Army Epidemiological Board, whose main interest lay in the investigation of methods for control of airborne infection with particular reference to the hemolytic streptococcus. The results of these two Commission projects are described elsewhere.[7] The third was the Army Air Forces Rheumatic Fever Control Program, Office of the Air Surgeon, which will be the subject of a later section of this chapter. These three programs were in active operation throughout 1944. Much new knowledge was acquired, but effective methods for the control of streptococcal disease and rheumatic fever were not forthcoming.

The Air Forces investigated intensively the role of sulfonamide prophylaxis during the early months of 1944. Streptococcal infection and rheumatic fever were notably reduced, and the use of this technique in certain defined situations, primarily for the prevention of these diseases, became established Army policy on 1 November 1944 with the publication of War Department Technical Bulletin (TB MED) 112. Unfortunately, by this time, strains of streptococci highly resistant to sulfonamides had emerged and were causing

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[6] Report, Chester S. Keefer, M.D., Director, and Lowell A. Rantz, M.D., Member, Commission on Hemolytic Streptococcal Infections, Army Epidemiological Board, April 1943, subject: Report of Investigation of Rheumatic Fever at Fort Francis E. Warren, Cheyenne, Wyo., Lowry Field, Denver, Colo., Buckley Field, Denver, Colo., and Camp Carson, Colorado Springs, Colo.

[7] (1) History of the Commission on Air-Borne Infections, Army Epidemiological Board, 1941–45. [Official record.] (2) Commission on Hemolytic Streptococcal Infections, Army Epidemiological Board. [Undated.] [Official record.]

disease among naval personnel where chemoprophylaxis had been widely used on a mass basis since December 1943.

Streptococcal infection continued to be epidemic throughout 1944, and 4,877 cases of rheumatic fever were reported in the United States. The highest incidence was again in the Sixth and Seventh Service Commands where 37 percent of the cases occurred. Twenty-four percent occurred in the States of Colorado, Utah, Wyoming, and Nevada, where relatively few troops were stationed. Streptococcal infection and rheumatic fever became an important problem among troops abroad for the first time in 1944 when 1,805 cases of the latter disease were reported. This represented a rate of only 0.47 per 1,000 per annum or approximately 38 percent of that among troops in the United States.

It became apparent, as the winter of 1945 began, that sulfonamide prophylaxis, the only method of proved value for the prevention of streptococcal infection and rheumatic fever, was no longer effective. Disease caused by resistant streptococci was epidemic in the U.S. Navy, and an outbreak of infection caused by similar strains had occurred at an Army Air Forces station. The entire problem was considered at a National Research Council conference on 28 February 1945. The failure of sulfonamide prophylaxis was detailed, and the hazards involved in its continued use were described. As a result of these experiences in the Navy, this technique was applied only selectively in the Army Air Forces and practically not at all in the Army Ground Forces. The possible value of penicillin prophylaxis was explored at another National Research Council conference on 20 March 1945, and studies for its evaluation under field conditions by the Army Air Forces were outlined but not undertaken.

The incidence of scarlet fever and rheumatic fever in the Army in the United States decreased in 1945 in spite of the absence of effective control measures. The incidence of streptococcal sore throat rose from 0.82 per 1,000 in 1944 to 3.64 in 1945. The effect was an increase in rate for the three conditions combined, from 3.98 per 1,000 in 1944 to 5.21 in 1945. Only 1,675 cases of rheumatic fever were reported. Two thousand and fifty additional cases occurred in the Army overseas. Another important National Research Council conference on streptococcal disease was held on 7 July 1945. The war ended in the autumn of that year, and information on the occurrence of this disease and rheumatic fever during demobilization is not available.

EPIDEMIOLOGY AND STATISTICS

Statistical and epidemiological data in regard to rheumatic fever and the causative hemolytic streptococcal infection has been presented in detail in another volume in the history of the Medical Department in World War II.[8]

[8] Medical Department, United States Army. Preventive Medicine in World War II. Volume IV. Communicable Diseases Transmitted Chiefly Through Respiratory and Alimentary Tracts. Washington: U.S. Government Printing Office, 1958.

This information will not be recapitulated, but a summary is appropriate. Of about 18,000 reported cases of rheumatic fever, 34 percent developed in troops stationed in the Seventh Service Command at a rate about six times the rate for the total Army. Hemolytic streptococcal respiratory disease was epidemic in all of the high incidence areas for rheumatic fever, and a direct relationship between infection by these organisms and the rheumatic state was established by critical investigations.

Approximately 23 percent of all rheumatic fever admissions occurred in troops overseas. The rate was about two-fifths of that in the continental United States. In terms of rates, the worst experiences were encountered in the European, Mediterranean, and Middle East theaters. Three reports describing the disease as it occurred in the North African, Mediterranean, and European theaters have been published.[9] The problem was much less in the China-Burma-India theater and in the Pacific and Latin American areas.

Rheumatic fever was most common in the months of January through June (77 percent of all cases) among men assembled for basic training, but occurred frequently during all seasons and among all types of personnel, particularly during the peak years of 1943 and 1944.

CLINICAL PICTURE

The clinical picture and natural history of rheumatic fever as it occurred among troops has been well defined in a few publications,[10] and in much greater detail in reports of the activities of Army and Air Force rheumatic fever centers.[11] These three reports, describing the disease as it was seen at Birmingham General Hospital, Van Nuys, Calif., Foster General Hospital, Jackson, Miss., and Torney General Hospital, Palm Springs, Calif., are most

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[9] (1) Bland, E. F.: Rheumatic Fever and Rheumatic Heart Disease in the North African and Mediterranean Theater of Operations, United States Army. Am. Heart J. 32: 545–559, November 1946. (2) Claiborne, T. S.: Rheumatic Fever and Rheumatic Heart Disease in a General Hospital in North Africa. Med. Bull. North African Theat. Op. (No. 5) 1: 8, May 1944. (3) Foster, R. F.: Rheumatic Fever Here and in the European Theater of Operations. Northwest Med. 45: 503–506, July 1946.

[10] (1) Wendkos, M. H., and Noll, J., Jr.: Symposium on Cardiovascular Diseases; A Survey of Rheumatic Fever in a Large Station Hospital. M. Clin. North America 28: 124–147, January 1944. (2) Wright, I. S.: Experiences With Rheumatic Fever in the Army. Bull. New York Acad. Med. 21: 419–432, August 1945. (3) Connor, C. A. R.: Experiences With Rheumatic Fever in the Army Air Forces. Am. J. Health 36: 236–243, March 1946. (4) Miller, J. H.: Rheumatic Fever at a Convalescent Center from March 1944 to March 1945. News Letter, Army Air Forces Rheumatic Fever Control Program, vol. 2, No. 10, p. 30, October 1945.

[11] (1) Report, Maj. Jules C. Welch, MC, Chief, Rheumatic Fever Section, Birmingham General Hospital, to The Surgeon General, attention: Director, Medical Consultants Division, 30 Nov. 1945, subject: Report on Studies on Rheumatic Fever. (2) Report, Capt. John F. McGinty, MC, Chief, Rheumatic Fever Section, Foster General Hospital, to The Surgeon General, attention: Director, Medical Consultants Division, 14 Dec. 1945, subject: Report on the Activities and Findings of the Rheumatic Fever Center, Foster General Hospital, Jackson, Mississippi, for the period from 2 Oct. 1944 to 1 Dec. 1945. (3) Report, Maj. E. P. Engleman, MC, Chief, Rheumatic Fever Center, Torney General Hospital, to The Surgeon General, attention: Col. Arden Freer, MC, Director, Medical Consultants Division, 11 Mar. 1946, subject: Report of Activities of Torney General Hospital Rheumatic Fever Center, 1 Mar. 1946.

complete. Data derived therefrom are presented in table 33. It should be remembered that these were essentially convalescent hospitals and that the acute phases of the illness were not observed by the officers preparing these reports. The information about the early stages of the illness were compiled from abstracts of the station hospital records which accompanied the patients. These were usually quite complete. Examination of other reports, and the extensive experience of the author in the field during this period, indicates that table 33 and the commentary which is to follow presents an accurate picture of rheumatic fever as it occurred during World War II in the Army.

TABLE 33. *Clinical and historical information on rheumatic fever as observed in three U.S. Army general hospitals*

[Percent expressed as percentages of cases in which the respective manifestations were observed]

Clinical data	Birmingham General Hospital (percent)	Foster General Hospital (percent)	Torney General Hospital (percent)
Past history of rheumatic fever	50. 4	41. 3	40. 6
History of preceding respiratory infection	54. 9	40. 1	84. 5
Extracardiac manifestations:			
Arthritis	100. 0	96. 7	98. 0
Chorea	(1)	. 5	. 2
Erythema multiforme or marginatum	5. 4	2. 2	2. 5
Erythema nodosum	2. 7	1. 8	(1)
Subcutaneous nodules	1. 5	1. 1	. 5
Pneumonia	3. 2	2. 5	3. 2
Cardiac manifestations:			
Apical systolic murmur	11. 8	13. 0	45. 0
Apical diastolic murmur	2. 7	8. 4	2. 5
Aortic insufficiency	10. 3	7. 7	5. 0
Pericarditis	5. 6	3. 3	3. 7
Cardiac insufficiency	0	. 6	1. 0
Electrocardiographic manifestations:			
Any abnormality	53. 5	27. 7	47. 6
Prolonged AV conduction	26. 8	24. 6	28. 2
Abnormal T waves	10. 1	3. 1	14. 0
Total number of cases	262	807	401

[1] Not recorded.

Striking differences between the rates of occurrence of various clinical manifestations, notably those referable to the heart, reflect differences in interpretation of physical and laboratory signs by medical officers in the various hospitals. Rheumatic fever in the Army was an arthritic disease. Almost 100 percent of cases exhibited subjective or objective evidence of joint involvement. This simply means that the nonarthritic form of the

disorder was rarely recognized. Detailed studies beginning with the initiating streptococcal infection revealed a considerable number of cases in this category.[12]

A past history of rheumatic fever was obtained in 40 to 50 percent of all cases. This demonstrates that persons who have had rheumatic fever are much more likely to develop another attack after streptococcal infection than are nonrheumatics. A preceding upper respiratory infection, sore throat, or scarlet fever had been recognized by about half of the patients. Nearly all hospitalized patients had fever and malaise in addition to arthritis, but many other clinical manifestations of rheumatic fever were uncommon. Epistasis, erythematous skin lesions, pericarditis, pneumonia, and subcutaneous nodules occurred infrequently, although very often more than one of these signs of severe rheumatic fever was demonstrated in the same patient.

Evidence of carditis was obtained frequently. During the acute phase of the illness, the most common sign was an abnormal electrocardiogram. Prolonged AV (atrioventricular) conduction was demonstrated in about one-quarter of all patients and unequivocal T-wave abnormalities in an additional 3 to 14 percent. The average percentage for all patients was approximately 7 percent. Other abnormalities were reported by two of these hospitals to bring the total presenting electrocardiographic evidence of carditis to about 50 percent. The significance of many of these minor changes in the tracings is questionable.

Arrhythmias of any kind were observed in less than 0.5 percent of cases. Cardiac insufficiency developed in less than 1 percent and was almost always of short duration. Only three deaths from active rheumatic fever with heart failure are recorded.

Cardiac murmurs were heard frequently, but the significance of many is difficult to assess. Apical systolic murmurs were discovered in 45 percent of cases in one hospital but in only about 12 percent in the other two. Apical diastolic murmurs were uncommon. Evidence of aortic insufficiency was obtained in 5 to 10 percent of this group of patients. It was often inferred that these lesions were the result of the episode of rheumatic fever under study. This was undoubtedly so in some, but the author examined a number of men in whom valvular disease was present at the onset of the attack and was a residuum of a previous rheumatic episode. The characteristic murmurs had been overlooked at the time of induction into the Army. The available data, obtained at convalescent centers, do not permit ready differentiation between these two different situations.

Carditis was present in 40 to 50 percent of all cases if only positive electrocardiographic abnormalities and clear-cut new murmurs are considered to be indicative of its presence.

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[12] Rantz, L. A., Boisvert, P. J., and Spink, W. W.: Hemolytic Streptococcic Sore Throat; The Poststreptococcic State. Arch. Int. Med. 79: 401–435, April 1947.

EARLY TREATMENT AND COURSE

Documentary evidence in regard to the usual early treatment of rheumatic fever in the Army is not available. Prior to the autumn of 1944, these patients were treated in station hospitals until convalescence was sufficiently established to permit return to duty, separation from service, or transfer to a regional general hospital. During this early period, treatment was the responsibility of the chief of medicine in each station hospital, and varied greatly from one to another.

Great interest had been aroused at about this time in the use of very large amounts of salicylates in the treatment of rheumatic fever. Regimens were widely employed in which every effort was made to administer 10 gm. per day of sodium salicylate. The drug was not often given intravenously in the Army, but significant toxicity was frequently encountered.

The other important phase of the treatment of rheumatic fever involved rest and this was regularly utilized but in widely differing degrees. Strict bed rest over long periods of time and until all clinical and laboratory signs of activity had vanished was usual. Often, fantastic limitations of activity were imposed, and patients were forbidden to feed, wash, or shave themselves for many weeks. As late as 1944, War Department Technical Bulletin (TB MED) 97, dated 29 September, warned that the head of the bed should not be raised during the period of active disease, since absolute recumbency was believed to be an important phase of treatment. No chemoprophylaxis of streptococcal infections was undertaken before 1944.

The response to rest and the administration of salicylates in these patients was almost always excellent. Fever and arthritis regularly melted away so that the patients ordinarily felt very well within 2 to 3 weeks, and restrictions to bed became difficult. More prolonged and difficult illnesses did occur, particularly in the presence of pericarditis, but such cases accounted for less than 5 percent of the total. Heart failure was virtually unknown and its management was not a significant problem. Only 1 death due to rheumatic fever with heart failure occurred in 1,470 cases admitted to convalescent centers (table 33). The only data in regard to the duration of laboratory evidence of activity are from the Torney General Hospital experience. The erythrocyte sedimentation rate (Wintrobe) became normal in an average of 11.2 weeks. It was elevated for more than 4 weeks in 59 percent and for more than 9 weeks in 34 percent of 401 cases. Abnormal rates persisted for more than 5 months in only 12 percent.

Treatment of early rheumatic fever was doubtless much better standardized after September 1944 when TB MED 97 was published. This directive recommended about 1 month of bed rest at the station hospital followed by transfer to a convalescent center by air. Sodium salicylate was to be given in a dose of 16 gm. during the first 24 hours, followed by 10 gm. per day. High blood levels of the drug were doubtless attained, but toxicity

must have been commonplace with this regimen. Continuous prophylaxis with daily administration of a sulfonamide was directed.

The usual treatment of rheumatic fever with prolonged and often absolute bed rest until clinical and laboratory evidence of quiescence was obtained produced results which were not entirely satisfactory because cardiac neurosis was a frequent complication. One group working at an Air Force center[13] utilized early ambulation in the treatment of 100 patients, continuing the administration of salicylates. The results were impressive in that the disease process subsided in the expected time without any increase in the incidence of chronic valvular heart disease. The experience of the author and his associates was similar in unpublished studies of a smaller group of patients.

LATE TREATMENT AND RESULTS

It was not until the middle of 1944 that much information became available in regard to the course of rheumatic fever in patients in the Army after the first few weeks of illness. Prior to this time, patients were separated from service, returned to duty after the disease had become quiescent, or forwarded to a general hospital. In the experience of the author, the first two events usually took place after about 6 months of treatment. Transfer to a general hospital was reserved for the very few patients whose disease was not ameliorated promptly or in whom the diagnosis was in doubt.

In Army Air Forces Letter 25–7, dated 29 April 1944, the Army Air Forces designated seven regional hospitals as rheumatic fever convalescent centers; namely, AAF Regional Station Hospital No. 1, Miami Area, Coral Gables, Fla.; Orlando Army Air Base, Fla.; Keesler Field, near Biloxi, Miss.; Davis-Monthan Field, Tucson, Ariz.; Las Vegas Army Air Field, Nev.; Hammer Field, Calif., and Santa Ana Army Air Base, Calif. In September 1944, the Army Service Forces followed suit and Birmingham, Torney, and Foster General Hospitals were so designated. All of these were in the southern part of the United States. The directives stated that patients were to be treated for about 1 month by bed rest and heavy salicylate therapy at the station hospital. At this time, it was anticipated that the acute manifestations of the disease would have subsided, and the patient was to be transferred by air to the center for additional rest and eventual rehabilitation. The number of available ambulance planes was not great, and it is not known how often this technique was employed. In the absence of air transport, patients were to be kept at the station hospital until fully convalescent and able to travel by train.[14]

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[13] Robertson, H. F., Schmidt, R. E., and Feiring, W.: The Therapeutic Value of Early Physical Activity in Rheumatic Fever. News Letter, Army Air Forces Rheumatic Fever Control Program, vol. 2, No. 10, p. 17, October 1945.

[14] Army Service Forces Circular No. 360, 1 Nov. 1944.

Very complete statements about the operations of the general hospital centers have been preserved,[15] and the following important facts about the late effects of rheumatic fever in troops have been obtained from them in addition to those that were used earlier in describing the nature of the acute illness.

Complete recovery without residua was the rule in these cases of rheumatic fever in young adults. Chronic valvular heart disease was the most serious complication. Table 33 shows that aortic insufficiency was demonstrated in from 5.0 to 10.3 percent; mitral stenosis in 2.5 to 8.4 percent; and mitral insufficiency in from 11.8 to 45.0 percent of all cases. Three difficulties arise in interpreting these data. One pertains to the varying diagnostic criteria that were applied, particularly in the recognition of mitral insufficiency. It is evident that these criteria were difficult to establish. They were less rigorous at Torney General Hospital than at the other two centers. A second stems from the fact that medical officers at the centers attributed all of the valvular disease present at the time of dismissal from the hospital to the current episode of rheumatic fever. There were many instances, as already indicated, when significant murmurs were present at the onset of the illness. These were certainly the result of previous attacks, the signs having been missed during the induction physical examination. No satisfactory data permitting detailed analysis of this important point are available. A third difficulty arises from the fact that the period of followup was short since it is known that clinical evidence of rheumatic valvular heart disease appears slowly and irregularly after an acute rheumatic episode.

One excellent study of 135 patients[16] has provided valuable information as to the outcome after a period of observation of 4 to 8 years. Followup physical examinations revealed no abnormalities in 75.4 percent. An additional 16, or 11.8 percent, had only an apical systolic murmur, believed by the author to indicate the presence of mitral insufficiency. It is probable that few of this latter group had significant valvular disease. Mitral stenosis, or aortic stenosis, or insufficiency were discovered in only 12.8 percent of these patients. It has been suggested that not all of these lesions were the result of the rheumatic fever which occurred during military service. Only three of the entire group had definite enlargement of the heart and none showed evidence of cardiac insufficiency. The signs described above had been present at the termination of the rheumatic attack in all but one case. Thus, there had been an extraordinarily low incidence of progression of heart disease during this long period of observation. Of the group, 15, or 11 percent, had experienced a rheumatic recurrence since separation from the service. Chemoprophylaxis was not employed in any case.

It is disturbing to learn that definite heart consciousness, or neurocirculatory asthenia, as evidenced by precordial pain, dyspnea, and palpitation was

[15] See footnote 11, p. 229.

[16] Engleman, E. P., Hollister, L. E., and Kolb, F. O.: Sequelae of Rheumatic Fever in Men: Four to Eight-Year Follow-Up Study. J.A.M.A. 155: 1134-1140, 24 July 1954.

present in one-third of these patients. Anxiety neurosis was a more common complication of rheumatic fever in these individuals than valvular heart disease. Only a few of the study group described were disabled and nearly all were in school or were employed.

It is generally believed that clinical recovery from rheumatic fever is accompanied by complete disappearance of pain in the joints. It is of great interest that this was not so in the Army. Persistent arthralgia was commonplace, having been noted in 50 to 60 percent of the cases and having continued for as long as 6 years.[17] Physical and roentgen examination of the joints never revealed any abnormalities after the first few weeks of the illness during which time effective salicylate therapy was instituted. The residual pain was often very disturbing to the affected individuals and interfered with resumption of their normal activity.

RECONDITIONING

Formal programs for the reconditioning of convalescent cases of rheumatic fever were not introduced in the Army until 1944 when treatment centers were established. Before this time, the station hospitals in areas where the disease was common were completely lacking in facilities for this purpose. Neither space, personnel, nor a suitable climate were available. This serious lack was an important contributing factor which led to the frequent appearance of cardiac neurosis. After the Army Service Forces and the Army Air Forces established centers, the situation improved greatly. Men were moved to these establishments fairly early in the disease, usually during the second or third month of illness.

Each of the centers located in general hospitals developed an elaborate program of supervised, graded, and gradually increased activity for convalescent patients. The official reports speak in glowing terms of the efficiency of these techniques. Complete recovery was hastened and cardiac neurosis minimized.[18] Reconditioning was also an important aspect of the treatment at the Army Air Forces rheumatic fever centers,[19] but information about results was not preserved. A formal study of the problem which was conducted in the physical fitness laboratory at Randolph Field, Tex., demonstrated that early activity proved to be safe and beneficial when accomplished with careful guidance and under the control of fitness tests.[20]

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[17] (1) See footnote 16, p. 234. (2) Starr, M. P., and Kimbro, R. W.: Residual Arthralgia in Rheumatic Fever Patients. News Letter, Army Air Forces Rheumatic Fever Control Program, vol. 2, No. 2, pp. 17-21, February 1945.

[18] See footnote 11, p. 229.

[19] Ershler, I.: Convalescent Program for Rheumatic Fever. News Letter, Army Air Forces Rheumatic Fever Control Program, vol. 2, No. 1, p. 1, January 1945.

[20] (1) Karpovich, P. V.: Physical Reconditioning of Rheumatic Fever Patients. News Letter, Army Air Forces Rheumatic Fever Control Program, vol. 2, No. 4, p. 14, April 1945. (2) Karpovich, P. V., Starr, M. P., Kimbro, R. W., Stoll, C. G., and Weiss, R. A.: Physical Conditioning After Rheumatic Fever. [Official record.]

DISPOSITION

The problem of disposition of patients who had had rheumatic fever was a knotty one during the early years of World War II, and formal guidance was not provided by The Surgeon General. Each hospital made its own policy based on the experience of its medical officers. In general, men were retained in service after recovery if there was no evident residual cardiac damage. Often, the severity of initial illness was also considered. Some hospitals were separating all men in whom the diagnosis of rheumatic fever was made because it was believed that the chance of recurrence was too great if these individuals were retained in the service. An attempt was made to make the policy more uniform by the publication of Circular Letter No. 144 by the Office of the Surgeon General on 7 August 1943. Discharge was recommended for all men with residual cardiac damage and retention in service of all others who had fully recovered. This policy, in the experience of the author, was not closely followed by officers in the field who frequently tailored it to fit individual cases.

Army Air Forces Letter 25–7 defined the disposition of rheumatic fever patients in the Army Air Forces and stated that those who had made a complete recovery without residua should be returned to full duty. Those with evidence of cardiac damage were to be discharged unless they possessed special skills in which case they could be retained in the service and marked for limited duty. Various special situations were also considered in detail. Data on disposition of 410 cases of rheumatic fever by an Army Air Forces center show that 53 percent were returned to duty. Of those discharged, 67 percent had had a recurrent attack or activity continuing for more than 3 months. Only 23 percent were separated from service because of residual cardiac changes. This was less than 10 percent of the whole treatment group. No comparable directives from the Army Service Forces have come to the attention of the author, and it is of interest that the official publication on rheumatic fever, TB MED 97, does not discuss the important problem of disposition; this was to be the subject of a subsequent directive which was never issued.

Uniform disposition was not accomplished even by the three general hospitals which served as rheumatic fever treatment centers.[21] At Birmingham General Hospital, the advice given in Circular Letter No. 144 was followed until September of 1945, and approximately 50 percent of the patients were discharged, the remainder being returned to limited duty. After that date, any evidence of carditis was accepted as grounds for separation. This included more than 80 percent of all cases. The staff at Foster General Hospital formulated its own policy and discharged all patients with multiple attacks of rheumatic fever in 1 year, those with any cardiac residua, and those whose disease remained active for more than 3 months. Approximately 50

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21 See footnote 11, p. 229.

percent of cases assigned to this hospital received certificates of disability for discharge. The medical officer in charge of the rheumatic fever center at Torney General Hospital believed that troops who had had rheumatic fever were unsuitable for further military service because of the great risk of recurrence. He arbitrarily recommended 80 percent of them for discharge.

In retrospect, it is difficult to understand why a uniform policy for disposition of rheumatic fever patients was not established for the Army Service Forces hospitals by The Surgeon General. The varying criteria for discharge from the service were unfair to the patients and created a sense of frustration and insecurity among the responsible medical officers who were constantly in doubt as to the proper course to follow.

CONTROL

Rheumatic fever control programs were not undertaken by the Army Service Forces, although intensive research was carried out by the commissions working under the auspices of the Army Epidemiological Board; centers for care and rehabilitation were established.

The Army Air Forces, on the other hand, originated a full-scale rheumatic fever control program under direct authority from the Commanding General, Army Air Forces, in the fall of 1943. Its objectives[22] were (1) recommendations for the use of sulfonamide prophylaxis for the control of respiratory infections and rheumatic fever, (2) adoption of uniform standards for the diagnosis of rheumatic fever, (3) coordination and standardization of bacteriological techniques in the study of the hemolytic *Streptococcus*, (4) establishment of a uniform convalescent program and followup studies on positive and suspected cases of rheumatic fever, and (5) consideration of special projects and investigations at various Army Air Forces posts.

All of these goals were accomplished with varying degrees of success. The greatest activity was in the area of study and control of streptococcal infection under objectives 1, 3, and 5. This work has been described in detail elsewhere.[23] Uniformity of diagnosis and treatment was accomplished partly by educational activities directed toward the staffs of station hospitals, but more directly by the creation of centers for the care of patients with rheumatic fever and the use of air transport permitting transfer to these institutions at an early stage of the disease. Much was accomplished by the wide distribution of a monthly newsletter published at the AAF Regional Hospital, Mitchel Field, Long Island, N.Y., with the support of the Josiah Macy, Jr. Foundation of New York and edited by Capt. (later Maj.) Charles A. R. Connor, MC.

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[22] The Denver Conference. News Letter, Army Air Forces Rheumatic Fever Control Program, vol. 1, No. 1, p. 2, August 1944.

[23] See footnote 8, p. 228.

Endless debate continued at various levels throughout the war in regard to the advisability of refusing induction to individuals with a past history of rheumatic fever because the number of such persons who developed recurrences of the disease was high. Mobilization Regulations No. 1–9 was variously modified. Between August 1940 and April 1944, active acute rheumatic fever or verified recurrent attacks of the disease in the past placed a man in the unacceptable group. The latter history was clearly not sought adequately by examining physicians at induction stations. In April 1944, the order was changed to include active acute rheumatic fever and verified single or recurrent attacks within 2 years. This order was not well designed since a definite attack of rheumatic fever has the same significance at any time in the life of the individual.[24]

RESEARCH

Clinical investigation of many phases of rheumatic fever was undertaken at numerous hospitals. The large amount of clinical material available to many highly skilled investigators permitted the rapid accumulation of information in regard to diagnosis, course, and treatment. Many reports of these studies were published but will not be reviewed here. The lack of special facilities in installations other than those specially supported by the Army Air Forces Rheumatic Fever Control Program or by the commissions of the Army Epidemiological Board prevented, for the most part, any fundamental work by these groups.

SUMMARY

Rheumatic fever was a common disease in the Army during World War II, particularly in certain geographic areas. It was observed in all degrees of severity, but the disease responded well to rest and the administration of salicylic acid and its derivatives. The course was usually monocyclic, and recovery in all but a few cases was complete within a few months. Valvular heart disease was a gratifyingly uncommon complication. The major problems encountered were those concerned with development of cardiac neurosis which was caused by overly severe restriction of activity, apprehension on the part of the medical officers in charge, and inadequate programs for convalescent rehabilitation. This situation was greatly improved during the last 2 years of the war by the creation of treatment centers.

Investigation of many aspects of the prevention and management of rheumatic fever was carried out. Much pertained to the study of the close relationship between infection by group A hemolytic streptococci and the rheumatic state and to measures for the control of streptococcal infection.

[24] It is certain that young adults who have had rheumatic fever are more likely to experience recurrences when exposed to streptococcus infection during military service than are nonrheumatics. They should be identified with care at the time of induction and a chemoprophylactic regimen instituted at once. This should permit them to contribute fully to the military effort.

CHAPTER IX

Meningococcal Infections

Worth B. Daniels, M.D.

HISTORICAL NOTE

Outbreaks of meningococcal infection are known to have occurred during all wars since the illness was first described by Vieusseux [1] in 1805. Important milestones in the development of knowledge of this disease can be briefly summarized. The isolation of the causative agent by Weichselbaum [2] in 1887 led to a search for a specific cure. Flexner and Jobling [3] thought that the antiserum prepared by them at the Rockefeller Institute in 1908 favorably modified the course of the disease.

Within 1 month of mobilization in World War I, the annual rate of admission to hospital for white enlisted men in the United States reached 1.71 per 1,000 troops, and within 7 months an explosive outbreak of meningococcal meningitis had begun (chart 12). In January 1918, the rate had risen to a peak of 4.48 per 1,000.[4] This epidemic afforded Herrick [5] an opportunity to study the use of antiserum under controlled conditions and to make observations on pathogenesis. His studies indicated that antiserum given intravenously reduced the mortality in patients with bacteremia and in those with meningitis. In spite of the use of meningococcal antiserum, however, there were 1,836 deaths among approximately 5,900 cases (31 percent case fatality ratio) among troops throughout the U.S. Army in a period of 33 months during and immediately following World War I.[6] Herrick's studies clearly showed that meningitis does not develop as the result of extension from the nasopharynx but begins as bacteremia with later localization in the meninges, joints, and other tissues. This concept has greatly influenced treatment and, together with the development of the sulfonamides, has been a factor in lowering the death rate.

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1 Vieusseux, M.: Mémoire sur la Maladie qui a règne à Génève au printemps de 1805. J. de méd., chir. et pharmacol. 11: 163–182, 1805.

2 Weichselbaum, A.: Ueber die Aetiologie der akuten Meningitis cerebro-spinalis. Fortschr. d. Med. Berlin 5: (No. 18), 573–583, 15 Sept. 1887; ibid., 5: (No. 19), 620–626, 1 Oct. 1887.

3 Flexner, S., and Jobling, J. W.: Serum Treatment of Epidemic Cerebrospinal Meningitis. J. Exper. M. 10: 141–203, January 1908.

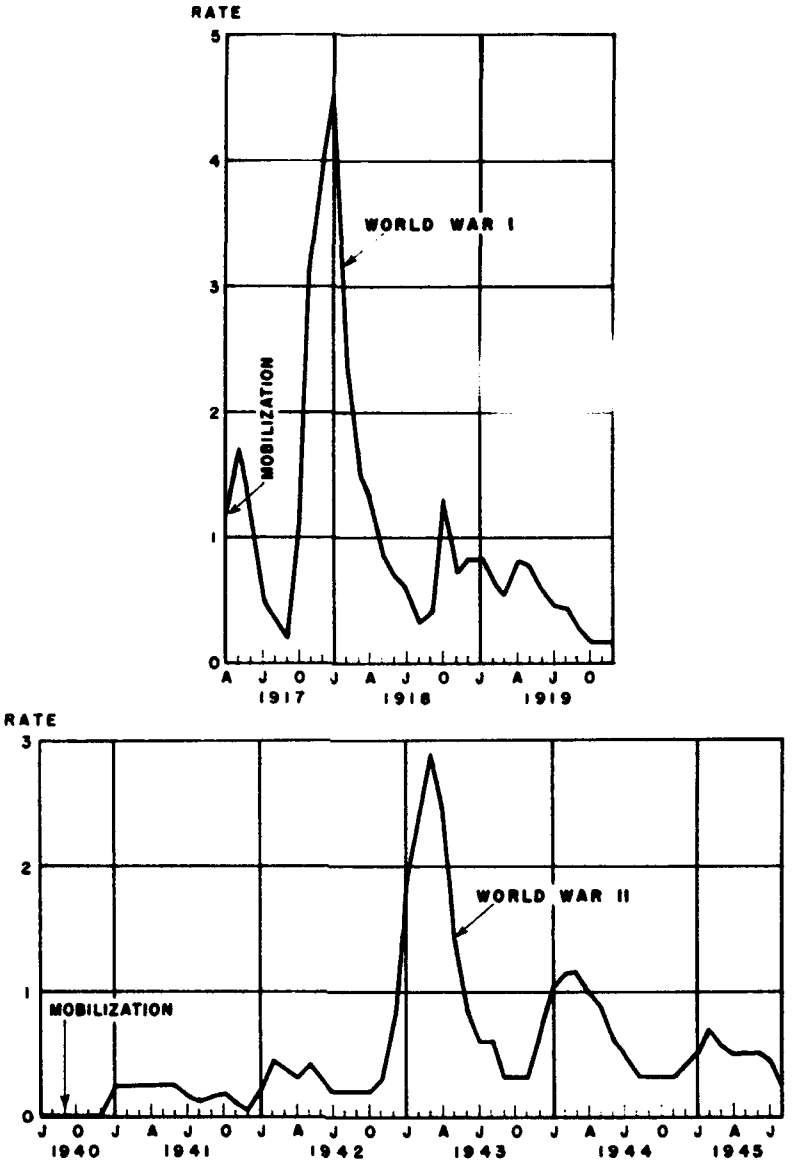
4 The Medical Department of the United States Army in the World War. Washington: U.S. Government Printing Office, 1928, vol. IX, pp. 203–221.

5 (1) Herrick, W. W.: The Epidemic of Meningitis at Camp Jackson. Preliminary report. J.A.M.A. 70: 227, 26 Jan. 1918. (2) Herrick, W. W.: Early Diagnosis and Intravenous Serum Treatment of Epidemic Cerebrospinal Meningitis. J.A.M.A. 71: 612–617, 24 Aug. 1918. (3) Herrick, W. W.: The Intravenous Serum Treatment of Epidemic Cerebrospinal Meningitis. Arch. Int. Med. 21: 541–563, April 1918.

6 See footnote 4.

CHART 12.—*Admissions to U.S. Army hospitals for meningococcal infections among troops in the continental United States, by month, World War I [1] and World War II [2]*

[Rate expressed as number of cases per annum per 1,000 average strength]



[1] The World War I rates represent primary admissions only and are limited to white enlisted men. These rates are from individual medical records as published in the official history of World War I.

[2] The World War II rates comprise secondary cases as well as admissions and are preliminary, based on the statistical health reports.

Sulfanilamide early proved to be a highly effective agent in the therapy of these infections.[7] In 1940–41, during the outbreak in Halifax, Nova Scotia, Dingle and his coworkers [8] showed the effectiveness of sulfadiazine in a small group of patients.

[7] Schwentker, F. F., Gelman, S., and Long, P. H.: The Treatment of Meningococcic Meningitis With Sulfanilamide; Preliminary Report. J.A.M.A. 108: 1407–1408, 24 Apr. 1937.

[8] Dingle, J. H., Thomas, L., and Morton, A. R.: Treatment of Meningococcic Meningitis and Meningococcaemia With Sulfadiazine. J.A.M.A. 116: 2666–2668, 14 June 1941.

INCIDENCE DURING WORLD WAR II

In World War II, mobilization began with the federalization of the National Guard in September 1940, and the induction of large numbers of selectees followed shortly. For over 2 years, only sporadic cases of meningitis occurred in troops. In December 1942, closely following an increase of respiratory disease in the late fall, the incidence of meningococcal infections rose sharply throughout Army installations in the United States. By March 1943, the outbreak had assumed severe proportions, and the incidence rate had reached 2.9 per 1,000 troops (chart 12). The rate among newly inducted soldiers was from 5 to 10 times greater than among soldiers with a year or more of Army service. At one post, where crowding among new inductees was excessive, the weekly rate rose to 42.2 per 1,000 per annum.[9]

Throughout 1943, the year of most numerous cases, data based on individual medical records show that 7,083 patients were admitted to hospitals with meningococcal infections; 6,370 of these developed the illness in the United States. The incidence rate per 1,000 per annum was 1.0 for the total U.S. Army, 1.2 for troops in the United States, and 0.4 for troops overseas.

For the year 1943, in the United States, the statistical health report rates per 1,000 per annum by service command are as follows:

Service Command	*Rate*
First	1.2
Second	1.6
Third	1.4
Fourth	1.5
Fifth	1.3
Sixth	1.5
Seventh	1.3
Eighth	.8
Ninth	1.0

The incidence of meningitis (0.8 per 1,000 per annum) in the European Theater of Operations, U.S. Army, during 1942 was greater than among troops in the United States. During 1943, the rate in the European theater remained about the same (0.9). In other oversea theaters, the rates in general rose somewhat, but no significant outbreaks occurred.

During September and October 1943, the incidence of meningococcal infections among Army troops in the United States fell nearly to the preepidemic level. A rise to a second, less elevated, peak began in the winter of 1943–44, with return to the preepidemic rate by summer. It is of some interest that the peak of the second rise (1.1 per 1,000 in February 1944) came 11 months after the height of the epidemic (2.9 in March 1943), table 34. In World War I, the second peak (1.2 admissions per 1,000 for white enlisted men in October 1918) occurred 9 months after the first peak (4.5

[9] Sartwell, P. E., and Smith, W. M.: Epidemiological Notes on Meningococcal Meningitis in the Army. Am. J. Pub. Health 34: 40-49, January 1944.

in January 1918).[10] The second rise in incidence among troops in the United States during World War II was as intense as that which occurred during World War I, and was more sustained. Attention is called to this because sulfonamides were widely used prophylactically in the fall and winter of 1943–44, following distribution of Circular Letter No. 170, Office of the Surgeon General, U.S. Army, dated 30 September 1943. This letter established as Army policy the administration of sulfadiazine to all newly inducted soldiers during the seasons when respiratory diseases were prevalent (chart 12).

Again, during the winter months of 1944–45, the admissions to hospital rose, but to a much less degree than during the previous winters.

TABLE 34.—*Incidence and deaths due to meningococcal infections, U.S. Army, World War I and World War II*

Period	Number of cases	Number of deaths	Case fatality ratio (percent)	Peak of incidence in the United States [1]	
				Period	Rate [2]
World War I (April 1917–December 1919):				World War I:	
Continental United States	[3] 2,878	986		January 1918	4.48
Total Army	[4] 5,839	1,836	31.4	October 1918	1.21
World War II (January 1942–December 1945):				World War II:	
Continental United States	10,619	410	3.9	March 1943	2.89
Total Army	13,922	559	4.6	March 1944	1.14

[1] The World War I data pertain to admissions for white enlisted men in the United States, whereas the World War II data represent incidence for all Army personnel in the United States.

[2] Rate expressed as number per annum per 1,000 average strength.

[3] Admissions only. Data on secondary cases are available only for enlisted men in the United States and Europe combined. Based on the distribution of admissions in the two areas, the incidence in the United States is estimated at 3,500 cases.

[4] Consists of admissions in the entire Army and secondary cases among enlisted men in the United States and Europe. Secondary cases among officers and among enlisted men outside the United States and Europe are not available, but the incidence is estimated to be 5,900 cases for the entire Army.

NOTE.—(1) Data for World War I were obtained from "The Medical Department of the United States Army in the World War." Washington: Government Printing Office, 1925, vol. XV, pt. 2. (2) Data for World War II are preliminary. (3) The number of deaths are from complete files of individual medical records, and incidence is based on sample tabulations of individual medical records, except for data on peak incidence which are from the statistical health report.

During the years 1942–45, in spite of the availability of highly effective treatment, meningococcal infections caused more deaths (559) than any other infectious disease, except tuberculosis. Table 35 shows the number of deaths in the U.S. Army during this period resulting from the more serious infectious diseases and the death rates from these diseases per 100,000 average strength.

[10] See footnote 4, p. 239.

Of 13,922 patients attacked by meningococcal infections during 1942–45, only 559 deaths were reported—a case fatality ratio of 4 percent During World War I, the ratio was nearly eight times as great, 31 percent. Chart 13 indicates the case fatality ratios in the continental United States by month during the two wars. The ratios for World War I are based on white enlisted patients in the continental United States.

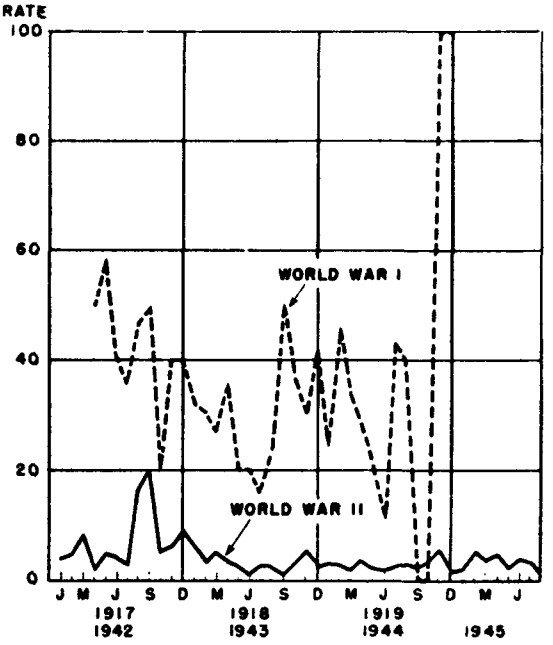


CHART 13.—*Case fatality ratios for meningococcal infections, by months, in the continental United States during World War I*[1] *and World War II*[2]

[1] The World War I ratios are presented in terms of numbers of deaths per 100 primary admissions for meningococcal infections among white enlisted men in the United States. During World War I for all enlisted men in the United States, the rate was 34 deaths per 100 admissions, or about 28 deaths per 100 cases in the United States.

[2] The World War II ratios are presented in terms of numbers of deaths per 100 cases (primary plus secondary cases) among all Army personnel in the United States.

TABLE 35.—*Comparative mortality of certain infectious diseases in the U.S. Army, 1942–45*

[Preliminary data, pending publication of final statistics]

[Rate expressed as number of deaths per annum per 100,000 average strength]

Cause of death	Rate 1942–45	Number of deaths				
		1942–45	1942	1943	1944	1945
Tuberculosis	3. 16	806	107	192	201	306
Meningococcal infections	2. 19	559	73	269	139	78
Bacterial pneumonia	1. 59	404	51	121	117	115
Lobar pneumococcal pneumonia	1. 41	358	51	121	91	95
Malaria	1. 19	302	25	113	89	75
Scrub typhus	1. 11	283	------	49	180	54
Poliomyelitis	1. 05	267	5	49	66	147
Infectious hepatitis	(1)	(1)	(1)	(1)	68	191
Primary atypical pneumonia	. 67	170	38	48	42	42
Diphtheria	. 48	123	1	10	22	90
Amebiasis [1]	. 15	39	6	4	7	22
Bacillary dysentery [1]	. 06	16	3	6	3	4

[1] Other infectious diseases causing more deaths than amebiasis were scarlet fever (61) and syphilis (70). Several other infectious diseases ranked higher than bacillary dysentery as a cause of death. Even though amebiasis and bacillary dysentery had low death rates, both were feared diseases.

The organization of medical care in the Army permitted the observation of early cases, resulting in better recognition of the various forms of the disease. It is, therefore, proposed in this chapter to describe the different forms that meningococcal infection assumed in soldiers during World War II, indicating how studies of the early stages contributed to knowledge of its pathogenesis, and to review the methods and results of treatment carried out in Army installations.

PATHOGENESIS

During nonepidemic periods, the rate for meningococcal carriers in troops ranged from 2 to 10 percent.[11] In periods of epidemic, carrier rates among troops rose and in studies made during the epidemic were reported as ranging from 23 [12] to 80 percent.[13] The carrier rate was lowest among newly inducted soldiers.

The micro-organism probably invades the body from the nasopharynx, and infection in this region may or may not be accompanied by evidences of respiratory infection. The subsequent manifestations are those of bacteremia and localization. Observations during World War II supported conclusions similar to Herrick's in World War I, since they clearly indicated that the course of events consisted of invasion of the bloodstream followed by localization in the meninges, skin, or other tissues of the body if not prevented by natural resistance or by therapy. The experience of all observers emphasized the necessity of viewing this disease as a bacteremia, which was sometimes overshadowed by the advent of the more dramatic symptoms of meningitis. By early recognition of the bacteremic stage and prompt institution of treatment, the infection might be terminated before its localization in the meninges or before it had become fulminating. If meningitis or other severe manifestation did, notwithstanding, supervene, the chance of recovery still was better than in cases that had not had prompt treatment. When medical officers became familiar with the disease, through experience in the epidemic, they recognized it in the bacteremic stage and prior to the advent of meningitis in as high as 30 to 40 percent of the patients.[14]

MENINGOCOCCAL BACTEREMIA

Prodromal symptoms.—The illness began, as a rule, with prodromal symptoms of disease of the upper respiratory tract. After an indefinite period

[11] Dingle, J. H., and Finland, M.: Diagnosis, Treatment and Prevention of Meningococcic Meningitis. With Résumé of Practical Aspects of Treatment of Other Acute Bacterial Meningitides. War Med. 2: 1-58, January 1942.

[12] Personal communication, C. T. Nelson, Fourth Service Command Laboratory, to the author.

[13] Cheever, F. S., Breese, B. B., and Upham, H. C.: The Treatment of Meningococcus Carriers With Sulfadiazine. Ann. Int. Med. 19: 602-608, October 1943.

[14] (1) Daniels, W. B., Solomon, S., and Jaquette, W. A., Jr.: Meningococcic Infection in Soldiers. J.A.M.A. 123: 1-9, 4 Sept. 1943. (2) Thomas, H. M., Jr.: Meningococcic Meningitis and Septicaemia: Report of Outbreak in the Fourth Service Command During the Winter and Spring of 1942-1943. J.A.M.A. 123: 264-272, 2 Oct. 1943.



FIGURE 35.—Rash in meningococcal bacteremia showing slightly raised pink macules with petechial centers, case 1.

of from a day to a week or more, the manifestations became more acute. There was usually a sudden chill with rapid rise in temperature, but the onset might be gradual. Malaise, extreme weakness, aching of muscles, moderate headache, nausea, vomiting, pain in joints, or acute inflammation of joints, developed. The most characteristic manifestation was the rash. Its presence was essential to clinical diagnosis before the advent of meningeal localization.

Rash.—The rash might be so sparse that careful and frequently repeated search was necessary to find it, or it might be obvious and noted by the patient. It appeared in a wide variety of forms, and knowledge of its variations was necessary to the recognition of the disease.

The commonest lesion was petechial or purpuric and varied from 1 to 15 mm. in diameter. In addition to this type, which has been emphasized in the past, other forms of rash, not commonly described, were generally seen. Ill-defined faint pink macules similar to the rose spots of typhoid fever were common. These might be evanescent, and not infrequently a scattered few constituted the only cutaneous manifestation. Maculopapular lesions (fig. 35) were usually present, and in some instances they had a central petechia. The larger ones of this type were nodular or plaquelike and often tender. When

on the extremities, these nodules bore a striking resemblance to the smaller lesions of erythema nodosum. Occasionally, there were petechiae in the conjunctivae and the oral mucous membranes.

Various combinations of the cutaneous manifestations occurred; indeed, most patients showed more than one type of lesion. The rash appeared anywhere on the body but usually spared the face and was less common on the palms and soles. It was often evident in crops. The macular lesions sometimes receded with fall in temperature, only to reappear as the temperature again rose. The rapidity with which the rash often appeared made it necessary to examine carefully every suspected patient at hourly intervals; in a few hours, it could advance from a few vague spots to a widespread eruption.

In fulminating bacteremia, a widespread extensive ecchymotic rash developed, involving, in some patients, as much as 80 percent of the body. In a few patients, large areas of hemorrhage developed beneath the conjunctivae and in the oral mucous membranes. Some of the ecchymotic lesions became vesicular, and ulceration occasionally occurred. The rapid disappearance of the maculopapular component of the rash within 12 to 18 hours after the beginning of therapy with sulfadiazine was almost diagnostic of meningococcal bacteremia.

Other symptoms.—Herpes simplex was common, usually occurring about the second day of illness. Herpes zoster, involving the ophthalmic and maxillary branches of the fifth cranial nerve, was observed in one patient.

At admission, the temperature of patients with meningococcemia ranged from 97° to 106° F. It was generally between 101° and 102° F.

Leukocytosis (15,000 to 50,000 per cubic millimeter), with an increase in polymorphonuclear cells, was the rule, but in a few patients the number of leukocytes was normal.

Variations in Meningococcemia

There was a simple acute form of meningococcemia with fever, malaise, painful joints, rash, and leukocytosis. The progress of this type could be arrested at this stage by therapy with sulfadiazine, as illustrated in case 1.

Case 1.—A soldier, aged 34, had had a slight cold for about 2 weeks before admission. During the afternoon of the day before admission he suddenly began to feel unusually tired and to ache all over. During the night he had chilly sensations alternating with feverishness, and on the morning of the day of admission he had a moderately severe headache. He was acutely, but not seriously, ill. His face was flushed and his temperature was 101.3° F. There was slight inflammation of the nose and throat, and a maculopapular rash (fig. 35) was scattered over the trunk and all extremities. Neurological examination gave entirely normal results. The leukocytes numbered 19,800 per cubic millimeter, with 81 percent polymorphonuclear cells. Blood cultured on admission yielded type I meningococcus. Lumbar puncture was not done. As soon as the blood for culture had been taken, sulfadiazine was given by mouth. The temperature was normal within 2 days. The patient developed no signs of meningitis.

The disease at times was relatively mild and subacute, so that the fever, malaise, painful joints, and rash suggested rheumatic fever or erythema multiforme. The following case is illustrative:

Case 2.—A soldier, aged 21, had been well until 3 days before admission, when he suddenly had a shaking chill with the development of fever, malaise, and sore throat. The only significant findings were a few erythematous blotches on the chest and the legs and a palpable spleen. There was a continuous fluctuating fever during the succeeding 11 days. A rash consisting of macular, papular, and nodular lesions, with a few petechiae, appeared in crops. These findings suggested erythema multiforme and erythema nodosum. Shortly after admission, redness, tenderness, and swelling of the right ankle developed. The leukocytes numbered 16,300 per cubic millimeter, with 73 percent polymorphonuclear cells. Many erythrocytes were noted in several specimens of urine. The spinal fluid was normal. Cultures of the blood yielded type IIa meningococcus. After the first dose of sulfadiazine by mouth, the temperature became normal and remained so. The rash faded promptly.

The extraordinarily mild character that meningococcal infection occasionally assumed is illustrated in case 3.[15]

Case 3.—The 10-year-old son of an officer was admitted to an Army hospital with minimal headache and fever (100° F.). Admission was granted only on the insistence of his apprehensive mother, who feared poliomyelitis. Because of pressure from the mother, examination of the cerebrospinal fluid and culture of the blood was made. The spinal fluid was normal. Two days later, cultures of both blood and spinal fluid that were made on admission grew meningococci. No specific treatment had been given. At this time, on careful scrutiny, one skin lesion thought to be a small petechial hemorrhage was found; a second examination of the spinal fluid showed a normal fluid and was sterile. Another culture of blood drawn on the third day again yielded meningococci. As the patient had become afrebrile and asymptomatic no sulfonamides were given. Subsequent cultures of the blood were sterile. For 10 days the patient was watched closely and developed no recurrence of symptoms and no manifestations of illness. At this time a course of therapy with sulfadiazine was administered. The patient was discharged well after approximately 3 weeks of observation.

It is probable that, during the periods of increased prevalence of meningococcal infection, some cases of mild character with spontaneous recovery were not detected. We know that recovery from meningococcal bacteremia has occurred after minimal amounts of sulfonamide, in some cases with a total dose of as little as 2 grams. These patients usually had a mild illness with fever and were given a single dose of sulfadiazine by the ward officer, after which no drug was administered. Later, the original cultures of blood taken before therapy were shown to contain meningococci, but the patients had by then become apparently well.

In other patients, the course was chronic and produced a persistent, low-grade, febrile illness, which in case 4 was not severe enough to prevent the performance of military duty.

Case 4.—A soldier, aged 23, was admitted to the orthopedic service because of an injured ankle. It was learned that for about 3 weeks he had been suffering from malaise, evening feverishness, and an intermittent eruption of red nodules on his legs. While in

[15] Personal communication, R. H. Turner, to the author.

the hospital his temperature ranged from 98.6° to 102° F. Migrating arthralgia was present, and a scattered erythematous papular rash appeared. This was most apparent on the extremities. The leukocytes numbered 12,000 per cubic millimeter, with 81 percent polymorphonuclear cells. Two cultures of the blood grew type I meningococcus. There were no meningeal symptoms or signs at any time, and the spinal fluid was normal. All manifestations cleared entirely within 24 hours after sulfadiazine was administered by mouth. The patient had been ill 4 weeks prior to treatment.

Transition From Bacteremia To Meningitis

The recognition of meningococcal infection before any evidence of invasion of the meninges was relatively easy during the epidemic, when the index of suspicion was high; it was in the sporadic case that delays in diagnosis and treatment were likely.

Case 5.—A private, aged 20, was admitted with a history of sore throat which had been present for 1 week. On the day before admission there was a sudden onset of shaking chills, fever, and painfulness of joints. A few small erythematous nodular lesions of the skin developed, and the pharynx showed mild inflammation. Both knees and both elbows and the right wrist and ankle were tender and hot—but not red or swollen. The leukocytes numbered 11,500 per cubic millimeter with 78 percent polymorphonuclear cells. A tentative diagnosis of acute rheumatic fever was made, and full dosage of salicylates prescribed. In spite of this medication the temperature ranged from 98.6° to 102.4° F. for the succeeding 13 days. On the 13th hospital day there was a sudden rise in temperature to 105° F., with severe headache, nausea, and vomiting. Within 3 hours the patient was stuporous and presented all of the signs of severe meningitis, with a dozen or so pinkish macules resembling rose spots on the trunk. The spinal fluid contained 1,200 leukocytes per cubic millimeter, with 95 percent polymorphonuclear cells. Treatment with sulfadiazine resulted in recovery. Blood was taken for culture after therapy was begun, and there was no growth.

Case 6 illustrates the importance of cutaneous manifestations, showing how the absence of a persistent rash during the greater part of the bacteremic stage delayed diagnosis.

Case 6.—The patient was admitted to the ward for patients with diseases of the respiratory tract, having had a cold with nasal congestion, slight cough, and sore throat for 1 week. During the day before admission, he had several slight chills and felt feverish; he vomited once. Examination revealed moderate inflammation of the nasopharynx, and a discrete macular rash on the trunk and around the shoulder girdle, which disappeared within a few hours after admission. For about 11 days the patient's temperature was of the septic type, with daily elevations to 102° F., associated with polymorphonuclear leukocytosis. The spleen was palpable. Since a diagnosis of subacute bacterial endocarditis was entertained, repeated cultures of the blood were made. Ten days after admission the temperature rose to 103° F. and the patient appeared worse. There were no meningeal signs or symptoms. On the next day, increasingly severe headache developed, with nausea and vomiting. Examination revealed a slightly stiff neck, positive Kernig's sign, and sparse petechiae on the upper part of the trunk. The spinal fluid was cloudy and contained 9,700 cells per cubic millimeter. Smear and culture of the fluid showed type I meningococcus. A culture of the blood taken on the day before the development of meningeal signs contained the same micro-organism. Recovery was rapid on therapy with sulfadiazine.

The speed with which meningitis could develop in a patient with meningococcemia was extremely variable. The next patient reported (case 7) was one in whom early meningitis was present on admission, as indicated by recovery of meningococci on culture from an otherwise normal spinal fluid. The history, however, gave clear-cut evidence that bacteremia had existed for about 24 hours before admission. This case also illustrates how rapidly meningitis can advance in spite of prompt and adequate therapy with sulfadiazine.

Case 7.—A private, aged 37, was well until the morning of the day before admission, when he suddenly had a shaking chill and began to feel extremely weak. Headache was moderately severe but subsided during the evening. On the morning of the day of admission the patient's headache was gone, but he noticed that he was covered with tiny dark purplish spots. His right knee was moderately painful on walking. Severe frontal headache again developed on his admission to the ward. He was obviously acute and seriously ill, although alert and well oriented. Scattered over the trunk and all extremities were myriads of dark petechiae, all less than 2 mm. in diameter. There was no stiffness of the neck, and Kernig's and Brudzinski's signs were not present. A specimen of spinal fluid contained 3 lymphocytes per cubic millimeter, a normal concentration of sugar, and a smear of it was negative for micro-organisms. By the following day, however, type I meningococcus grew in the culture of this fluid. Immediately after the initial lumbar puncture, 5 gm. of sodium sulfadiazine (in 1,500 cc. of saline and dextrose solution) was given intravenously.

Four hours after admission the patient developed projective vomiting and rapidly became stuporous. All the signs of meningitis were present. Five and one-quarters hours after the first lumbar puncture another specimen of spinal fluid was obtained. The fluid was under greatly increased pressure and contained 17,700 leukocytes per cubic millimeter, with 99 percent polymorphonuclear cells. The concentration of sugar had fallen to a level too low to read with accuracy and the level of sulfadiazine had reached 8.2 mg. per 100 cubic centimeters. Smear and culture of this second specimen were negative for meningococci in spite of the addition of para-aminobenzoic acid to the culture media. After an extremely stormy course, the patient recovered.

Although the culture of blood on admission was contaminated and no meningococci were found, the history of a shaking chill, the presence of a purpuric rash extensive enough to be noticed by the patient, and a painful knee joint—all at a time when the patient was entirely free of headache—were believed to be evidence that invasion of the bloodstream occurred several hours before admission. That meningitis was in the earliest phase at the time of admission was shown by the fact that the spinal fluid was normal in every respect except that meningococci were grown on culture. There were no meningeal signs except severe headache.

FULMINANT MENINGOCOCCAL BACTEREMIA

Without adrenal hemorrhage.—A form of fulminant, rapidly fatal meningococcal infection occurred, with little or no evidence of meningitis either during life or at necropsy, and without the clinical manifestations of the Waterhouse-Friderichsen syndrome, while the adrenals, at necropsy,

showed no abnormality. The rash was widespread and frequently as extensive as that seen in patients who had massive bilateral hemorrhage into the adrenals. The following is a case in point:

Case 8.—A 20-year-old soldier was admitted at 4:30 a.m. after an illness of a few hours, with chills, fever, headache, and weakness. On admission the temperature was 107° F. Stupor was marked. The pulse was strong, pounding, and rapid. The blood pressure was 120 systolic and 70 diastolic. There was no stiffness of the neck or other evidence of meningeal irritation. Widely scattered over the skin were myriads of petechial and purpuric lesions, some of which coalesced to form areas of ecchymosis. The cerebrospinal fluid was normal. A culture of the blood later grew type I meningococcus. Sodium sulfadiazine, 4.0 gm., was promptly given intravenously. Stupor deepened, and only terminally did cyanosis develop. Death occurred 8 hours after admission.

At autopsy neither the adrenals nor the leptomeninges showed abnormalities. There were small scattered hemorrhages throughout most of the organs.

Instances of a fatal form of fulminating bacteremia associated with so-called tubular degeneration of the adrenal cortex, as described by Rich,[16] occurred among Army personnel. The adrenals in these patients were not the site of hemorrhage. These cases occurred with and without meningitis. The following case, reported by Kinsman, D'Alonzo, and Russi,[17] is illustrative:

Case 9.—A 29-year-old white soldier was admitted to the hospital at 3:30 p.m. on 22 January 1944, about 2 hours after sudden onset of weakness, shaking chills, fever, headache, pain in the back, and exhaustion. The temperature on admission was 104.6° F. The leukocytes numbered 11,950, with 84 percent neutrophils. Physical examination revealed nuchal rigidity of minimal degree, but Kernig's sign was absent. The pharynx was moderately injected. Type I meningococcus was later recovered from the spinal fluid. Early the next morning (23 January) the patient developed an increasingly widespread, mottled purpuric and ecchymotic rash over the entire body, including the face and neck. About 80 percent of the surface of the body eventually became involved. There were scattered hemorrhagic spots, most of them large, an inch or more in diameter. These were also observed in the conjunctivae and mouth; the uvula was completely black from hemorrhage. In spite of treatment, the eruption continued to spread. The patient became restless, complaining of chilliness, and of the burning and soreness of the eruption. His lips, fingernails, and entire skin became cyanotic, the pulse was 110, and blood pressure was 130 systolic and 100 diastolic. Nuchal rigidity had not increased and Kernig's sign was still absent. The leukocytes numbered 27,200, with 87 percent neutrophils. The temperature was 105° F. At 1:10 p.m. he became comatose and markedly cyanotic, with rapid respirations. The temperature climbed to 107.8° F., and the respirations dropped to 8 per minute. A direct smear of his blood showed diplococci lying within the cytoplasm of the neutrophils. The culture of the blood was later reported positive for type I meningococcus. The patient expired at 3:10 p.m., 26 hours after onset. A second spinal puncture was done at the time of the necropsy and showed 2,200 cells.

Necropsy revealed widespread focal hemorrhages in the pulmonary parenchyma and petechial hemorrhages in the pleura, pericardium, and endocardium. Examination of the adrenals showed no gross hemorrhages. Microscopically, there was marked congestion

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[16] Rich, A. R.: A Peculiar Type of Adrenal Cortical Damage Associated With Acute Infections, and Its Possible Relation to Circulatory Collapse. Bull. Johns Hopkins Hosp. 74: 1–15, January 1944.

[17] Kinsman, J. M., D'Alonzo, C. A., and Russi, S.: Fulminating Meningococcic Septicemia Associated With Adrenal Lesions; An Analysis and Discussion of Seven Cases. Arch. Int. Med. 78: 139–169, August 1946.

of the sinusoids but no extravasation of blood. The cells in the glomerular zone displayed a vacuolated cytoplasm, and appeared of average size, while those in the inner part of the fascicular and reticular zones had shrunk, their cytoplasm being homogeneous, dark, and sprinkled with brown pigment. In this case the tubular changes in the outer half of the fascicular layer were prominent. The lesion was similar to that described by Kich. The cords in the outer third of the fascicular zone were converted into tubules lined by vacuolated cells, many of which had undergone degeneration with fraying of the cytoplasm and pyknotic changes of the nuclei. In some instances, the adrenal cells had disappeared entirely from the inner layer of the cortex, leaving only a reticular stroma between the congested capillaries. The medulla was not abnormal.

The meninges were not conspicuously involved on gross examination. Microscopically, there was a fair amount of acute inflammatory cellular exudate in the subarachnoid spaces.

Fulminating meningococcal bacteremia, without meningitis, occurred with the clinical manifestations of the Waterhouse-Friderichsen syndrome, and yet no hemorrhage or other abnormality of the adrenals was found at necropsy. Four such cases were found among 300 fatal cases analyzed (table 36).[18] In a number of others, the history suggested this syndrome, but the case abstracts were not full enough to allow reliable deductions. Thomas [19] has reported 3 such cases in a series of 49 fatal cases.

TABLE 36.—*Cause of death* [1] *in 300 cases of meningococcal infection reviewed at the Armed Forces Institute of Pathology*

Cause of death	Number	Percent
Fulminating bacteremia:		
Without adrenal hemorrhage [2]	30	10
With adrenal hemorrhage [3]	126	42
Total	156	52
Meningitis	144	48
Total	300	100

[1] With renal complications (estimated case fatality in the total U.S. Army, 0.01 percent) in three cases, due to sulfonamide therapy.

[2] Four of these patients showed the clinical manifestations of the Waterhouse-Friderichsen syndrome.

[3] Five of these patients did not exhibit the clinical manifestations of the Waterhouse-Friderichsen syndrome.

Case 10.—A soldier, aged 21, suddenly became ill 24 hours before admission with severe headache, stiffness, generalized aching, nausea, and vomiting. On examination, aside from fever, dusky cyanosis, and petechiae scattered over the skin, no other deviation from normal was found. About 18 hours after admission, in spite of a concentration of 9 mg. percent of sulfadiazine in the blood, the patient became rapidly worse. The skin eruption spread and pallor, with cyanosis, became extreme. The extremities were clammy

[18] Daniels, W. B.: The Cause of Death in Meningococcic Infection: An Analysis of 300 Fatal Cases. Am. J. Med. 8: 468 473, April 1950.

[19] Thomas, H. M., Jr.: The Treatment of Fulminating Meningococcic Infections. Bull. U.S. Army M. Dept. No. 73, pp. 78 84, February 1944.

and there was evidence of marked shock. A culture of blood was positive for meningococci. Stained films of blood from the fingertip showed diplococci within the leukocytes; smears from punctured purpuric skin lesions revealed gram-negative diplococci. The patient died in shock 30 hours after admission.

Necropsy showed no adrenal hemorrhage or evidence of meningitis. Petechiae were scattered over all serous surfaces. The interstitial tissues of the myocardium showed a diffuse infiltration with polymorphonuclear leukocytes.

The records of 300 of the soldiers who died as the result of meningococcal infection between September 1940 (mobilization) and 31 December 1945 were reviewed at the Army Institute of Pathology (now the Armed Forces Institute of Pathology), Washington, D.C. (table 36). Ten percent were cases of fulminating bacteremia without adrenal hemorrhage. Of these, 13 had no meningitis, 16 had slight meningitis, and the autopsy record of 1 was incomplete. The average duration of life after admission to hospital was 33 hours, ranging from 2 to 101 hours. Four of these patients satisfied all the clinical criteria of the Waterhouse-Friderichsen syndrome, but at autopsy, the adrenals were not abnormal. The average duration of life in these 4 cases was 40 hours from time of admission to hospital.

With adrenal hemorrhage.—Fulminating meningococcal bacteremia with peripheral vascular failure and hemorrhage into the adrenals evident at necropsy—the so-called Waterhouse-Friderichsen syndrome—was described first in 1894 by Voelcker.[20] Additional cases were later reported by the authors whose name the syndrome bears.[21] No more dramatic or catastrophic situation requiring immediate therapy can face the physician.

From the beginning of the epidemic, patients with this syndrome were admitted to Army hospitals. Some died before specific treatment was instituted. In the analysis of 300 fatal cases, it was found that in 121 cases (40 percent) death was due to this form of infection. (Five additional cases in this series had adrenal hemorrhage without the clinical syndrome (p. 254).) In view of the rarity of this disease, it is not surprising that, of the whole series of 126 fatal cases with adrenal hemorrhage, 14 (11 percent) came to necropsy lacking correct diagnosis. Ante mortem, these were classified as follows: Rocky Mountain spotted fever, 3; heat stroke, 2; purpura hemorrhagica, 2; endemic typhus, 1; acute leukemia, 1; pachymeningitis, 1; and no diagnosis, 4. A few more than 100 instances of this form of meningococcal infection had been reported in the world literature before World War II.

In two published series of 214 and 182 patients with meningococcal infection, the Waterhouse-Friderichsen syndrome occurred in 3.3 and 2.2 percent, respectively.[22] As noted, the records of the 300 cases studied at the

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[20] Voelcker, A. F.: Pathological Report. Abstract. Middlesex Hospital Reports, 1894, p. 279.

[21] (1) Waterhouse, R.: A Case of Suprarenal Apoplexy. Lancet 1: 577-579, 4 Mar. 1911. (2) Friderichsen, C.: Nebennierenapoplexie bei kleinen Kindern. Jahrb. f. Kinderh. 87: 109-125, 1818.

[22] (1) See footnote 17, p. 250. (2) Bernhard, W. G., and Jordan, A. C.: Bilateral Adrenal Hemorrhage (Waterhouse-Friderichsen Syndrome) Associated With Meningococcal Septicemia: Report of Four Cases in Adults With a Review of the Literature. J. Lab. & Clin. Med. 29: 357-365, April 1944.

Armed Forces Institute of Pathology showed that 126 (42 percent) of the soldiers with adrenal hemorrhage died (table 36). More than 50 instances of this syndrome were reported in the literature by U.S. Army Medical Corps officers. This is an incomplete list as many cases were described only because of unusual features, long survival period, or recovery.[23]

Meningitis was usually absent or extremely slight in these patients. In analysis of the 126 cases of fulminating bacteremia with adrenal hemorrhage, no post mortem evidence of meningitis was found in 61; in 48, the meningitis was early and minimal; in 7, it was moderately severe; in another 7, severe; in 3 cases, the grade of meningitis was not clear from the records. Early death may have been responsible for the slight degree or absence of meningeal inflammation.

Clinical course.—As with other meningococcal infections, prodromal respiratory symptoms usually preceded the onset. These were followed by general aching, painful joints, headache, weakness, nausea, vomiting, chills, and fever. Within a few hours there was a dramatic, sudden change, with the development of apprehension, restlessness, and often an initial delirium. At a later stage, there were frequent lucid intervals. A previously insignificant rash suddenly became widespread, purpuric, and ecchymotic, and often covered two-thirds of the body. The conjunctivas and buccal mucous membranes showed hemorrhages. As a rule, there were no signs of involvement of the meninges, but meningitis, usually of mild degree, might be present. Cyanosis, low blood pressure, rapid, thready or imperceptible pulse, cold, wet extremities, and all evidences of extreme shock supervened. Anuria with retention of nitrogen was usual. Within a few hours to a day or more, pulmonary edema usually supervened, and death generally occurred in spite of heroic therapy. In fatal cases, the average duration of life from admission to death was 24 hours.[24]

A classical instance of this clinical course follows.

Case 11.—A 21-year-old soldier developed headache, weakness, general aching, and vomiting 1½ hours before admission to hospital at 5 p.m. on 17 April 1943. By midnight,

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[23] (1) Wright, D. O., and Reppert, L. B.: Fulminating Meningococcemia With Vascular Collapse (Waterhouse-Friderichsen Syndrome): Report on Four Adult Patients Who Recovered. Arch. Int. Med. 77: 143-150, February 1946. (2) Kasich, M., and Disick, S.: Meningococcemia With Bilateral Adrenal Hemorrhage (Waterhouse-Friderichsen Syndrome): Report of Two Cases. J. Tennessee M.A. 36: 464-467, December 1943. (3) Marangoni, B. A., and D'Agati, V. C.: Hepatorenal Failure in the Waterhouse-Friderichsen Syndrome: Clinico-Pathologic Observations in Two Cases With Prolonged Survival Periods. Am. J.M. Sc. 207: 385-393, March 1944. (4) D'Agati, V. C., and Marangoni, B. A.: The Waterhouse-Friderichsen Syndrome. New England J. Med. 232: 1-7, 4 Jan. 1945. (5) Park, F. R., and Taplin, G. V.: Meningococcic Meningitis With Waterhouse-Friderichsen Syndrome. Report of a Case With Recovery. [Official record.] (6) Felder, S. L., and Stacy, A., Jr.: Meningococcemia With Waterhouse-Friderichsen Syndrome. [Official record.] (7) Leichliter, J. W., and Fish, C. E.: The Waterhouse-Friderichsen Syndrome: A Report of a Case in a Soldier. Mil. Surgeon 93: 77-81, July 1943. (8) Bush, F. W., and Bailey, F. R.: The Treatment of Meningococcus Infections With Especial Reference to the Waterhouse-Friderichsen Syndrome. Ann. Int. Med. 20: 619-631, April 1944. (9) Potter, H. W., and Bronstein, L. H.: The Waterhouse-Friderichsen Syndrome; Report of a Case Terminating in Recovery. J. Lab. & Clin. Med. 29: 703-708, July 1944.

[24] See footnote 18, p. 251.

fever of 106° F., a purpuric skin eruption, and an irrational mental state had developed. Because of obvious meningococcal bacteremia, 4 gm. of sodium sulfadiazine was given parenterally. By 5 a.m. on 18 April, he was stuporous, cyanotic, cold, and in collapse, with a pulse rate of 160 and blood pressure of 70 systolic and 35 diastolic. In spite of large doses of sulfadiazine, adrenal cortical extract, dextrose, sodium chloride and plasma, the purpuric rash spread and large areas of ecchymosis developed (fig. 36). Circulatory collapse increased, the pulse became imperceptible, and the blood pressure fell to 40 systolic and 0 diastolic. Coma developed. The patient died, in pulmonary edema, 36 hours after admission and 26 hours after the institution of specific therapy. There had been no clinical evidence of meningitis and the patient's condition did not warrant spinal puncture. The cerebrospinal fluid at autopsy contained two cells and was sterile. Cul-



FIGURE 36. Widespread ecchymotic rash in a patient with fulminating bacteremia and hemorrhages into the adrenals, case 11.

tures of the blood during life contained meningococci, and many micro-organisms were seen in leukocytes in smears of the peripheral blood and of purpuric lesions of the skin. Chemical analyses of the blood were as follows: Nonprotein nitrogen 75, creatinine 1.7, chlorides 478, sugar 126, sulfadiazine 20 mg. per 100 cubic centimeters. Autopsy revealed massive hemorrhage in both adrenals and no evidence of meningitis.

Waterhouse-Friderichsen syndrome.—The analysis shown in table 37 suggests that the grade of adrenal hemorrhage has a direct relationship to duration of life. There is, however, ample evidence that shock and circulatory collapse incident to fulminating bacteremia may occur without adrenal hemorrhage. As has been stated, fulminating infection with no evident adrenal abnormality at autopsy (case 10) can produce a clinical picture identical with the classical Waterhouse-Friderichsen syndrome. (See also table 36.) Profound injury to other organs as a result of toxemia and widespread hemorrhage, frequently with marked cellular infiltration of the myocardium,

might well be the sole cause of death. Marangoni and D'Agati,[25] following observation of two patients with long survival periods (80 and 88 hours), have expressed the opinion that there are two distinct stages in the Waterhouse-Friderichsen syndrome: First, the phase of profound shock and circulatory collapse; if this is survived, the second, or hepatorenal, phase begins. Clinically, it is characterized by marked oliguria with azotemia, and pathologically, by severe central necrosis of the liver associated with changes in the glomeruli and tubules of the kidney. A number of observers[26] believe that circulatory collapse in the Waterhouse-Friderichsen syndrome is primarily the result of widespread hemorrhages and changes in tissue, rather than of adrenal insufficiency secondary to hemorrhage into these glands. It is pointed out that (1) in this condition death requires but a few hours, whereas adrenalectomized animals live for several days; (2) classical clinical manifestations of the Waterhouse-Friderichsen syndrome can occur in patients with fulminating bacteremia without abnormality of the adrenals at necropsy; (3) conversely, among the 126 patients found to have had adrenal hemorrhage at necropsy, in 5 the clinical manifestations were not those of the Waterhouse-Friderichsen syndrome[27] (table 36); (4) some recovered patients had been given no adrenocortical hormone; and (5) in patients who recovered, the discontinuation of adrenocortical hormone after a few days did not lead to a recurrence of symptoms. If there were adrenal insufficiency secondary to hemorrhagic destruction of the adrenals in these cases, such temporary therapy would scarcely have been curative.

Accordingly, although the severity of adrenal hemorrhage appears in direct correlation with the length of life in the series of fatal cases shown in table 37, it cannot be assumed that there is a direct causal relation between them. The severity of the adrenal lesion may be regarded rather as an index of the severity of the whole pathological process, in which it occurs as an end result.

The Waterhouse-Friderichsen syndrome before the development of sulfonamides was invariably fatal. In 1945, Weinberg and McGavack collected from the literature 11 instances of recovery and reported an additional case with recovery.[28] Thirteen other patients who recovered have been either Army personnel or cases observed by the author.[29] Undoubtedly, a number

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[25] See footnote 23 (3), p. 253.

[26] (1) See footnotes 17, p. 250; 19, p. 251; and 23 (1)and (3), p. 253. (2) Thomas, H. B., and Leiphart, C. D.: Septicemia and Purpura With Adrenal Hemorrhage in Adult (Waterhouse-Friderichsen Syndrome); A Discussion of the Role Played by the Adrenal Gland in the Production of the Syndrome; Report of Two Adult Cases. J.A.M.A. 125: 884-890, 29 July 1944.

[27] See footnote 18, p. 251.

[28] Weinberg, L. D., and McGavack, T. H.: Waterhouse-Friderichsen Syndrome; Report of Case With Recovery. New England J. Med. 232: 95-101, 25 Jan. 1945.

[29] (1) See footnotes 17, p. 250; and 23 (1), (4), (5), (6), (8), and (9), p. 253. (2) Wechsler, H. F., and Rosenblum, A. H.: Meningococcic Meningitis. Mil. Surgeon 95: 132-135, August 1944. (3) Meyer, R. R.: Meningococcal Meningitis; A Report of Thirty-Three Cases With No Deaths. New England J. Med. 230: 452-455, 13 Apr. 1944.

of additional cases were not reported. Probably some of the recovered patients, although clinically examples of the Waterhouse-Friderichsen syndrome, actually had fulminating bacteremia without adrenal hemorrhage, but when a patient has recovered, there is no way to ascertain the nature or location or extent of tissue damage that was associated with the clinical syndrome.

TABLE 37.—*Severity of adrenal hemorrhage and duration of life in 126 of 300 fatal cases of meningococcal infection*

Grade of hemorrhage	Number of cases	Percent	Number of cases with relevant data	Number of hours from admission to death		
				Average	Maximum	Minimum
Mild	21	16. 7	20	48	120	1¾
Moderate	47	37. 3	44	22	60	⅙
Massive	56	44. 4	53	16	49	1
Not recorded	2	1. 6	1	53	53	53
Total	126	100. 0	118	24	120	⅙

MENINGOCOCCAL MENINGITIS

Although it was clearly demonstrated in many patients that meningococcemia preceded the onset of meningitis, the commonest type of meningococcal infection in all Army installations was that exemplified by case 12. Here, the results of meningeal involvement were so dramatic as to overshadow completely those of bacteremia. Bacteremia and meningitis set in almost simultaneously.

Case 12.—A soldier, aged 20, was admitted in violent delirium. The history obtained after the patient had improved indicated that he had been perfectly well until the evening of the day before admission, when severe occipital headache suddenly developed, with a feeling of great fatigue. During the night, pain in the left elbow and ankle began. Early on the day of admission he lost consciousness and regained it only after 12 hours of treatment in the hospital. Examination revealed a gravely ill patient, who had many small erythematous macules scattered over the trunk and extremities. Several of the lesions were hemorrhagic. There was pronounced rigidity of the neck, positive Kernig's and Brudzinski's signs, and slight weakness of the right side of the face. The leukocytes numbered 18,800 per cubic millimeter with 80 percent polymorphonuclear cells. Culture of the blood was later reported as sterile; the spinal fluid showed 9,900 leukocytes per cubic centimeter, of which 99 percent were polymorphonuclear cells. Gram-negative intracellular diplococci were seen on smear, and type I meningococcus was present on culture of the spinal fluid. Immediate therapy with sulfadiazine resulted in complete recovery.

The review of 300 of the fatal cases of meningococcal infection showed that 144 (48 percent) were classified as dying of meningitis (table 36). Only

6 of these patients came to necropsy without correct diagnosis, as follows: No diagnosis, 2; endemic typhus, 1; malaria, 1; pachymeningitis, 1; and psychosis, 1. It is of interest that only 26 of the 144 patients lived 96 hours or longer after admission to hospital. The average duration of life of the 118 patients who lived less than 96 hours was 36 hours, the range being from 1 to 95 hours (table 38). Since meningococcal meningitis itself, before the use of sulfonamides, rarely killed in so short a period, one might reasonably expect other lesions due to the meningococcal infection to play some role. Of the 118 patients who died within 96 hours after admission, evidence of lesions other than those in the meninges was reported in 62. Certain lesions associated with the death of those patients are listed, as follows:

Lesions	*Number of patients*
Pneumonia	26
Encephalitis	11
Myocarditis	11
Pressure cone	4
Purulent pericarditis	4
Periadrenal hemorrhage	1
Tubular degeneration of adrenals	1
Meningococcal peritonitis	1
Purulent arthritis	1
Subarachnoid hemorrhage	1
Bleeding peptic ulcer	1
Total	62

A pressure cone was noted 4 times, myocarditis 11 times, and pneumonia 26 times. Encephalitis was found in 11 cases, its occurrence indicating an organic basis for the changes in personality occasionally reported in patients who recover from meningitis. It seems probable that the majority died of the concomitant bacteremia with toxemia or some complication.

TABLE 38.—*Duration of life in relation to severity of illness in 118 of 144 cases of meningitis studied at the Armed Forces Institute of Pathology*

Severity of lesion	Number of cases	Percent	Number of cases of known duration	Number of hours from admission to death		
				Average	Maximum	Minimum
Moderate	10	8	10	23	62	1
Severe	93	79	93	38	95	1
Not recorded	15	13	10	30	90	2
Total	118	100	113	36	95	1

The duration of life in relation to severity of meningitis in the patients who lived less than 96 hours after admission to hospital is shown in table 38.

Those patients with a moderately severe grade of meningitis died on the average of 15 hours earlier than those classified as severe on the basis of spinal fluid and autopsy findings. This is additional evidence that these patients died from bacteremia before the meningitis had reached severe proportions.

Among the 144 cases of meningitis studied at the Armed Forces Institute of Pathology, the cause of death of the 26 patients who lived longer than 96 hours is shown, as follows:

Meningitis	9
Meningoencephalitis	3
Pneumonia and meningitis	4
Sulfonamide nephrosis	3
Adrenal infarction	1
Myocarditis	1
Brain abscess due to *Neisseria intracellularis*	1
Hemoglobinuric nephrosis after transfusion	1
Pulmonary infarction	1
Multiple lung abscesses	1
Recurrent fulminating meningococcal sepsis	1

The duration of life ranged from 4 days to 4 months: 10 died on the 5th day of illness, 3 on the 7th, 2 on the 8th, 3 on the 9th, 2 on the 10th, 1 on the 11th, 1 on the 13th, 1 on the 15th, and the other 3 lived 1, 1, and 4 months, respectively. It is seen that only 9 of these 26 patients died of meningitis alone (1 patient was treated inadequately beginning on the 7th day of disease, and sulfonamides were stopped in 1 after good response because of assumed drug fever). Three patients died of myocarditis, brain abscess due to *Neisseria intracellularis*, and pulmonary infarction after recovery from meningitis. It will be noted that there was no instance of chronic basilar meningitis or of hydrocephalus, the common sequelae of meningococcal meningitis in the past.

COMPLICATIONS

In the various series of cases of meningococcal meningitis reported during World War II, complications of the disease occurred in approximately 10 percent. The most common were transient paralyses of the fourth, sixth, seventh, and eighth cranial nerves. Herpes zoster involving the trigeminal nerve appeared in one patient. Aside from occasional residual nerve deafness and a rare instance of persistent diplopia, these lesions cleared completely with recovery. Paralysis of the serratus anterior was reported.[30]

In fulminating bacteremia, electrocardiograms were rarely made because of the critical condition of the patient and the emphasis placed on needed therapy. However, two instances of changing electrocardiograms with T-wave inversions and abnormalities in the S–T segment have been de-

30 See footnote 14, p. 244.

scribed.[31] Both patients recovered. Sudden and unexpected death from myocarditis occurred in one patient after apparent recovery from meningitis. In this case, Holman reported marked degenerative changes throughout one-third of the myocardium at necropsy. Myocarditis of significant grade was present at necropsy in 28 of 126 fatal cases with adrenal hemorrhage. Bronchopneumonia terminally was not uncommon. Optic atrophy, corneal ulceration, conjunctivitis due to *N. intracellularis*, pericarditis, and osteoperiostitis have each been noted in published reports.

Spontaneous glycosuria at onset was reported as occurring in one-third of 26 patients with meningococcal meningitis,[32] but rarely among Army personnel during the Second World War.[33] It may be accompanied by ketosis, hyperglycemia, and diminished sugar tolerance. Coma with glycosuria and ketosis at the onset of meningitis might lead to the erroneous diagnosis of diabetic acidosis.

In meningococcemia, inflammatory joint affections occurred in from one-third to one-half of the cases. These were usually simple inflammatory reactions but occasionally effusion into the joint, and rarely pyarthrosis developed. The latter required aspiration, but surgical drainage was not necessary in any reported case during the Second World War. Residual joint stiffness, persisting for some weeks after recovery, was noted.[34]

Some of the ecchymotic skin lesions ulcerated, but sloughing of large ecchymotic lesions rarely occurred. These were slow to heal. In almost all fatal cases of bacteremia and many of meningitis, pulmonary edema and effusion into the pleural sacs were terminal complications of the illness.

Renal complications of meningitis are discussed in the section on treatment.

OTHER MENINGOCOCCAL INFECTIONS

Only one instance of meningococcal pneumonia was reported during World War II.[35] This followed 5 weeks after a classical attack of primary atypical pneumonia. The patient developed severe, diffuse pneumonia with high fever. The sputum on two occasions contained about 75 percent meningococci (proved bacteriologically and serologically) and 25 percent hemolytic streptococci, group A. The course of the disease, ending in recovery, was apparently not influenced by the adequate doses of sulfadiazine given. The patient gave no evidence of bacteremia or meningitis.

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[31] (1) Rappaport, J. N., and Zuckerbrod, M.: Recovery From Fulminating Meningococcic Infection With Myocarditis Proved by Electrocardiography. J. Lab. & Clin. Med. 30: 307-316, April 1945. (2) Holman, D. V., and Angevine, D. M.: Meningococcus Myocarditis; Report of Two Cases With Anatomical and Clinical Characteristics. Am. J.M. Sc. 211: 129-137, February 1946.

[32] Ferguson, F. C., and Barr, D. P.: Glycosuria in Meningitis. Ann. Int. Med. 21: 173-186, August 1944.

[33] (1) See footnote 17, p. 250. (2) Federer, J. J.: Glycosuria and Hyperglycemia Associated With Acute Meningitis; Report of a Case. New England J. Med. 233: 342-343, 20 Sept. 1945.

[34] See footnote 15, p. 247.

[35] Roberg, N. B.: Meningococcic Pneumonia. Bull. U.S. Army M. Dept. 4: 97-99, July 1945.

Thirteen cases of proved meningococcal conjunctivitis were described among U.S. Army personnel during World War II.[36] All occurred during the period of increased incidence of meningococcal infection, and only one was associated with bacteremia or meningitis. The response of all these patients to therapy with sulfadiazine was excellent.

LABORATORY DIAGNOSIS

In meningococcal infections, the assistance of the laboratory in arriving at the correct etiology and confirming the clinical diagnosis was directly proportional to the adequacy of methods of culture, the care with which studies were carried out, and the cooperation between the wards and the laboratory. At the beginning of the epidemic, laboratory officers in the Army hospital, like the clinicians, had had relatively little experience in the study of this disease. The standard operating procedure consisted of directing the ward nurse or attendant to send the tubes of cerebrospinal fluid obtained from the patient to the laboratory for examination. The laboratory, as a rule, made no great speed in examining this fluid or inoculating media. Under these conditions, the percentage of positive cultures and of bacteriologically confirmed diagnoses was not enviable. As the number of cases rose, however, there was rapid improvement in this situation in most hospitals, with better coordination between the clinician and the laboratory. In some hospitals, a representative of the laboratory came immediately to the bedside when a lumbar puncture was to be done. Inoculations with blood and cerebrospinal fluid were made directly into previously warmed culture media, and these were promptly incubated in proper atmosphere. The improvement in results was striking. With this method, it was possible to achieve bacteriological confirmation in 95 percent of the patients who had not received treatment with sulfonamides prior to obtaining material for smear or culture.[37]

The micro-organisms isolated from patients during the outbreak have, as is usual in these infections, been predominantly type I. The distribution of types of meningococci recovered by the Fourth Service Command Laboratory from 1,436 known cases of meningococcal infections from August 1942 to December 1945[38] is shown in table 39.

In the majority of patients ill with the Waterhouse-Friderichsen syndrome or with fulminating sepsis, careful examination of films of blood taken from the fingers for differential counts revealed diplococci within the leukocytes. Smears and cultures made from petechial, purpuric, or even

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[36] (1) Bauer, C. E., Gall, E. A., and Cox, C. D.: Meningococcal Conjunctivitis; Report of Three Cases. Mil. Surgeon 95: 24-27, July 1944. (2) Theodore, F. H., and Kost, P. F.: Meningococcic Conjunctivitis. Arch. Ophth. 31: 245-247, March 1944. (3) Reid, R. D., and Bronstein, L. H.: Meningococcic Conjunctivitis. J.A.M.A. 124: 703, 11 Mar. 1944. (4) Thygeson, P.: Primary Meningococcic Conjunctivitis Treated by Sulfadiazine. Am. J. Ophth. 27: 400-401, April 1944.

[37] See footnote 14 (1), p. 244.

[38] See footnote 12, p. 244.

macular skin lesions showed meningococci in many instances. Tompkins[39] obtained positive cutaneous smears in 39 of 48 cases. In some patients, smears showed bacteria at a time when culture of the blood was sterile. Bernhard and Jordan[40] compared the results of concomitant examination of smears and cultures of material from purpuric lesions with cultures of the blood and of the spinal fluid in 40 patients. The smears from the purpuric lesions were positive in 68 percent and the cultures in 88 percent, while the cultures of the blood and cerebrospinal fluid were positive in 75 and 82 percent, respectively.

TABLE 39.—*Distribution of types of meningococci in 1,436 cases of meningococcal infection, Fourth Service Command Laboratory, August 1942–December 1945*

Types of meningococci	Number	Percent
Group I	1,288	89.7
Group II	27	1.9
Group IIa	108	7.5
Polyvalent [1]	13	.9
Total	1,436	100.0

[1] Includes micro-organisms with the biological characteristics of meningococci that agglutinate in polyvalent antimeningococcal serum but not in group-specific serum.

The importance of careful bacteriological studies should not be underestimated. However, during an outbreak of meningococcal infection, the diagnosis of bacteremia can and must be made on clinical grounds long before there is any report of culture of the blood if one hopes to prevent meningitis or fulminant infection. The finding of diplococci in leukocytes in smears of blood or smears from purpuric lesions is of importance, but in patients with rash the clinical impression of a trained observer should be relied upon in instituting treatment. Since, during the epidemic, 92 percent of the patients with meningococcal meningitis showed a characteristic rash,[41] a high degree of diagnostic accuracy could be attained on purely clinical grounds. In neither meningitis nor bacteremia should initiation of treatment be delayed by waiting for laboratory reports.

TREATMENT

At the beginning of the epidemic, although Circular Letter No. 170 had been issued, there was little standardization of treatment in U.S. Army hospitals. To a great extent, this was due to the dearth of published reports

[39] Tompkins, V. N.: The Diagnostic Value of Smears From Purpuric Lesions of the Skin in Meningococcic Disease. J.A.M.A. 123: 31-32, 4 Sept. 1943.

[40] Bernhard, W. G., and Jordan, A. C.: Diagnosis of Meningococcic Infections, Use of Material From Skin Lesions. Mil. Surgeon 95: 405-409, November 1944.

[41] See footnote 14 (1), p. 244.

on the use of sulfadiazine in large groups of patients with meningitis, to difficulties in obtaining the drug, and to the inability of some installations to acquire the sodium salt of sulfadiazine. Early cases were treated with sulfanilamide, sulfapyridine, sulfathiazole, or sulfadiazine alone or in conjunction with antisera or antitoxin. Thomas,[42] of the Fourth Service Command, reported a mortality of 20 percent in 40 cases treated during the first week of the epidemic (the week ending 1 January 1943) and 8.8 percent in 317 cases early in the epidemic. However, during February and March 1943, this was lowered to 2.1 percent in 761 cases. The fall in mortality was not the result of a decrease in virulence of the micro-organism. While 108 soldiers were being treated in one Army hospital in the Fourth Service Command with a mortality of less than 3 percent, there were 4 deaths among 8 civilians in the same county. The early high mortality was probably due to inexperience of the medical officers with the disease and delay in instituting treatment. Correction of these conditions was prompt, with dramatic reduction in mortality.

Meningococcemia.—The treatment of soldiers with simple meningococcemia became relatively standardized in Army installations and was highly effective. Under clinical observation, it became obvious that those with uncomplicated meningococcemia who were treated early did not require large doses of sulfadiazine. An initial dose of 4 gm. was given followed by 1 gm. every 4 hours until the temperature had been normal for at least 2 days. Parenteral administration was resorted to in patients who were vomiting.

Renal complications.—Treatment of patients with meningitis varied somewhat at different Army hospitals. Massive dosage of sulfadiazine reaching more than 20 gm. in the first 24 hours [43] was used, with the achievement of concentrations in the blood of 18 to 24 mg. percent. Among 134 patients so treated, complications of therapy (86 percent of which were renal) occurred in 28 percent. At another hospital, a loading dose (of sodium sulfadiazine) of 0.1 gm. per kilogram of body weight was given intravenously in 1,000 cc. of isotonic sodium chloride solution. Following this, one-half the initial dose was given parenterally every 8 hours until the patient could retain the drug by mouth. Concentrations in the blood and cerebrospinal fluid of 13 and 11 mg. percent, respectively, were obtained with excellent therapeutic results. However, gross hematuria occurred in 15 percent and anuria in 6.6 percent of the patients. When dosage was reduced to 0.05 gm., followed by 0.025 gm. per kilogram of body weight 4 hours later, and the latter dose repeated every 8 hours thereafter, no renal complications were noted.[44] With this dosage, the average concentrations of sulfadiazine in the blood and spinal fluid were 8.5 and 6.5 mg. percent, respectively. In

[42] See footnote 14 (2), p. 244.

[43] (1) Ochs, L., Jr., and Peters, M.: Management of Meningococcic Infections at the Station Hospital, Fort Benning, Ga. War Med. 4: 599-605, December 1943. (2) Kaplan, G.: Massive-Dose Sulfadiazine Therapy in Meningococcus Meningitis. New York State J. Med. 43: 2210-2212, 15 Nov. 1943.

[44] See footnote 13, p. 244.

this connection, it is of interest that Dowling and Lepper [45] reported that no urinary calculi appeared in their patients with pneumonia when the concentration in the blood did not exceed 9.2 mg. percent.

Ochs and Peters,[46] while treating patients with an initial intravenous dose of 10 gm. of sodium sulfadiazine in 5 percent solution, encountered renal complications in 5 of 23 patients. Later, 2,000 cc. of ⅙ molar sodium lactate was given intravenously before administering the sulfadiazine with the complete elimination of renal complications.

Drug of choice.—Sulfanilamide, sulfathiazole, and sulfapyridine were used early in the epidemic because of the scarcity of sulfadiazine. The latter became the standard drug for treatment because of its efficiency and relatively low toxicity. Sulfanilamide retained an important place in therapy until penicillin became available. When gross hematuria, renal colic, oliguria, or anuria developed during sulfadiazine therapy, sulfanilamide was an effective substitute, since its use was not associated with the deposition of acetylated material in the urinary tract.

In analyzing the records of 300 of the patients who died of meningococcal infection,[47] only 3 instances of death as a result of sulfonamide medication were found. All of these were due to renal complications caused by therapy. Since it can be assumed that virtually all patients who received any specific treatment were given sulfonamides, the case fatality ratio from complications of therapy with sulfonamides in the 13,922 cases treated during the Second World War was estimated to be about 0.04 percent (the total mortality from renal complications). This is astounding when one considers that massive dosage was administered to very ill, and often seriously dehydrated, patients. No death from hemolytic anemia or agranulocytosis was encountered.

Since the close of World War II, other sulfonamides have proved curative. Gantrisin has been shown to be effective in two small series of cases of meningococcal infection.[48] It has the virtue of greater solubility and, in consequence, rarely causes renal complications. If extensive trials justify the promise of this drug, it may be preferred to sulfadiazine. Its dosage is similar to that of sulfadiazine.

Fulminating infections.—The treatment of soldiers with fulminating bacteremia and with the Waterhouse-Friderichsen syndrome may be considered together as, in general, their treatment was identical. Among the 300 deaths analyzed, 156 patients died of fulminating meningococcal bacteremia, 126 with and 30 without adrenal hemorrhage (table 36). Of these, 30 had

[45] Dowling, H. F., and Lepper, M. H.: Toxic Reactions Following Therapy With Sulfapyridine, Sulfathiazole and Sulfadiazine. J.A.M.A. 121: 1190-1194, 10 Apr. 1943.

[46] See footnote 43 (1), p. 262.

[47] See footnote 18, p. 251.

[48] (1) Brickhouse, R. L., Lepper, M. H., Stone, T. E., and Dowling, H. F.: The Treatment of Pneumonia and Other Infections With a Soluble Sulfonamide, Gantrosan (NU-445; 3,4-dimethyl-5-sulfanilamido-isoxazole). Am. J.M. Sc. 218: 133-137, August 1949. (2) Rhoads, P. S., Svec, F. A., and Rohr, J. H.: Bacterial Meningitis: Results of Treatment in Seventeen Cases With a New Sulfonamide (Gantrisin). Arch. Int. Med. 85: 259-264, February 1950.

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had no specific therapy, 98 were treated with sulfadiazine, 14 with other sulfonamides, and in 14 there was no record of treatment. Penicillin was given concurrently with sulfadiazine to at least 16 patients. The records concerning antiserum, antitoxin, and extracts of adrenal cortex were not adequate for analysis.

Thomas,[49] early in the epidemic, stated that the three major objectives of treatment were to combat bacteremia, toxemia, and shock. He advocated 3 to 5 gm. of sodium sulfadiazine intravenously with 1,000 cc. of ⅙ molar sodium lactate and the maintenance of a concentration of sulfadiazine in the blood of 10 to 15 mg. percent. Intravenous administration of 20,000 units of meningococcal antitoxin was advised as an initial dose, followed by the same amount every 4 hours until 100,000 units had been given. Plasma, isotonic sodium chloride, and aqueous extract of adrenal cortex in large doses (30 cc.) at frequent intervals was advocated. In instances where pulmonary edema supervened, it was suggested that 500 cc. of 1.5 percent solution of sodium chloride containing 25 gm. of dextrose be given. A goodly number of patients were treated by a regimen of this type with certain variations. Many received no antitoxin and others either insignificant amounts of adrenocortical extract or none. In the treatment of 13 recovered cases of the Waterhouse-Friderichsen syndrome, the only constant and recurrent features of therapy were the administration of sulfadiazine in adequate amounts, intravenous isotonic sodium chloride and dextrose, and oxygen. Penicillin, adrenocortical extract, desoxycorticosterone acetate, plasma, adrenalin, adrenalin in oil, meningococcal antitoxin, or antimeningococcal serum were given in some. It would appear from the description of treatment that recovery occurred in any case where early adequate antibacterial therapy and proper antishock measures were carefully carried out. The major objective was very early recognition of bacteremia with prompt treatment before the infection became fulminating.

Cortisone, which has become available since World War II, offers an additional potent agent in combating the adrenal insufficiency incident to adrenal hemorrhage. Too few instances of its use have been recorded clearly to evaluate its place in therapy. However, its use in the Waterhouse-Friderichsen syndrome with adrenal hemorrhage is rational, in view of its proved value in critical episodes occurring in Addison's disease with complicating infection. The number of circulating eosinophils should be determined to assist in differentiating this syndrome from fulminating bacteremia without adrenal hemorrhage; the former may show more, and the latter less, than 50 cells per cubic millimeter. Therapy with cortisone should consist of an additional dose of 200 mg. divided into four 50 mg. doses injected intramuscularly into four separate sites to hasten absorption.[50] Subsequent

[49] See footnote 19, p. 251.

[50] (1) Personal communication, P. H. Forsham, to the author. (2) Forsham, P. H., and Thorn, G. W.: The Diagnosis and Treatment of Adrenal Cortical Insufficiency. Veterans Admin. Tech. Bull. TB 10-62, pp. 1-23, 30 Mar. 1950.

dosage may be guided by following the level of circulating eosinophils. These should be kept at 15 per cubic millimeter or below.[51] This will probably require 50 mg. or more every 6 hours for the first 2 days and 25 mg. at the same interval for the next 3 days. Thereafter, the dose should be gradually reduced and discontinued over the period of 1 week.

Potent new pressor agents have become available since the Second World War. Norepinephrine by continuous intravenous infusion has proved helpful in maintaining blood pressure and combating shock in two instances of the Waterhouse-Friderichsen syndrome.[52]

Serum

In meningitis, antimeningococcal serum in conjunction with sulfadiazine was employed intravenously and occasionally intrathecally in some hospitals.[53] Serum was often given to patients who had not shown an adequate response to therapy with sulfonamide 36 to 48 hours after the initiation of treatment. It became rapidly apparent, however, that patients treated with sulfonamides alone fared as well as those to whom serum was given in addition.[54]

Antitoxin

Meningococcal antitoxin, originally advocated by Ferry[55] and used extensively by Hoyne,[56] was given to a few patients with meningitis, especially those with fulminating infections. In the early period of the epidemic, antitoxin was employed in some installations, particularly those in the Fourth Service Command, in patients ill with fulminating bacteremia. At 10 station hospitals, 134 patients were treated with this material. It was thought by Thomas[57] that benefit was observed in 56 of these patients. In retrospect, it appears that mortality in cases of fulminating bacteremia treated with antitoxin is not lower than in cases treated with sulfadiazine alone. The excellent therapeutic results with sulfadiazine alone led the Council on Pharmacy and Chemistry of the American Medical Association

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51 Faloon, W. W., Reynolds, R. W., and Beebe, R. T.: The Use of the Direct Eosinophil Count in the Diagnosis and Treatment of Waterhouse-Friderichsen Syndrome. New England J. Med. 242: 441-445, 23 Mar. 1950.

52 (1) Personal communication, P. B. Beeson, to the author. (2) Unpublished observations of the author.

53 (1) See footnote 43 (1), p. 262. (2) Borden, W. B., and Strong, P. S.: Epidemic Meningitis; A Report of 15 Cases at Fort Eustis, Virginia. Mil. Surgeon 91: 517-522, November 1942. (3) Kasich, M., and Shulman, B.: Thirteen Cases of Meningitis Treated With Serum and Sulfonamides at Station Hospital, Fort Dix, New Jersey. Mil. Surgeon 90: 419-424, April 1942.

54 See footnote 14 (2), p. 244.

55 Ferry, N. S.: Meningococcus Antitoxin; Prophylactic and Therapeutic Tests on Guinea Pigs. J. Immunol. 23: 315-324, October 1932.

56 Hoyne, A. L.: Intravenous Treatment of Meningococcic Meningitis With Meningococcus Antitoxin. J.A.M.A. 107: 478-481, 15 Aug. 1936.

57 See footnote 19, p. 251.

to remove antimeningococcal serum and meningococcal antitoxin from the accepted preparations listed in "New and Nonofficial Remedies." [58]

Penicillin

During the early period of the war, penicillin was in its experimental stage and not in sufficient production for use in treatment of meningococcal infections. Beginning late in 1943, small amounts first became available at some Army hospitals for the treatment of patients with this infection. TB MED (War Department Technical Bulletin) 9, dated 12 February 1944, first advocated the use of penicillin in conjunction with sulfadiazine in patients with fulminating infection and in those who failed to respond to, or should not receive, sulfadiazine. Therapy both intrathecally and by the usual parenteral routes was advised in meningitis.

There were relatively few published reports on the use of penicillin in meningococcal infections. Kolmer [59] reported that in 96 collected cases treated by intravenous, intramuscular, and intrathecal injections, the mortality was about 8.5 percent. Of these 96 cases, 76 were described by Drs. D. H. Rosenberg and P. A. Arling, who stated that 75 recovered, a death rate of 1.3 percent. This is comparable to the mortality in similar series of patients treated with sulfadiazine.[60] Although the reports from the Army [61] do not represent studies of the use of this antibiotic in large numbers of patients, they quite clearly indicate its place in therapy.

Rammelkamp and Keefer [62] found no penicillin in the cerebrospinal fluid after constant intravenous administration over a 24-hour period, and as a result of their observations, the intrathecal together with other parenteral routes have been used in patients with meningitis. Rosenberg and Sylvester [63] reported the finding of penicillin in the spinal fluid in patients with meningitis, and Price and Hodges reported the cure of four patients, following intramuscular and intravenous administrations alone.

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[58] Status of Antimeningococcic Serum and Meningococcus Antitoxin; Report of the Council on Pharmacy and Chemistry. J.A.M.A. 124: 95, 8 Jan. 1944.

[59] Kolmer, John A.: Penicillin Therapy. New York: D. Appleton-Century Co., Inc., 1945, p. 202.

[60] (1) See footnote 14 (1), p. 244. (2) Hill, L. W., and Lever, H. S.: Meningococcic Infection in an Army Camp. J.A.M.A. 123: 9-13, 4 Sept. 1943.

[61] (1) Kinsman, J. M., and D'Alonzo, C. A.: Meningococcemia; A Description of the Clinical Picture and a Comparison of the Efficacy of Sulfadiazine and Penicillin in the Treatment of Thirty Cases. Ann. Int. Med. 24: 606-617, April 1946. (2) Kinsman, J. M., and D'Alonzo, C. A.: The Penetration of Penicillin Through Normal and Inflamed Meninges. New England J. Med. 234: 459-463, 4 Apr. 1946. (3) Letter, Lt. Col. J. Murray Kinsman, MC, Chief, Medical Service, Regional Hospital, Fort Bragg, N.C., to The Surgeon General, 27 Mar. 1945, subject: Transmittal of Report [Penicillin Studies]. (4) Rammelkamp, C. H., and Kirby, W. M. M.: Factors Determining the Dosage of Penicillin in the Treatment of Infections. Bull. New York Acad. Med. 21: 656-672, December 1945. (5) Dotterer, J. E.: A Fatal Case of Meningococcal Meningitis Treated With Sulfadiazine and Penicillin. ETO Med. Bull. 31: 36-38, May-June 145. (6) Lo Vetere, A. A.: Penicillin's Application to Meningitis, Meningococcemia and Septicemia. Kentucky M.J. 43: 24-27, January 1945. (7) Price, A. H., and Hodges, J. J.: Treatment of Meningitis With Penicillin Injected Intravenously and Intramuscularly. New York State J. Med. 44: 2012-2014, 15 Sept. 1944.

[62] Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion, and Distribution of Penicillin. J. Clin. Investigation 22: 425-437, May 1943.

[63] Rosenberg, D. H., and Sylvester, J. C.: The Excretion of Penicillin in the Spinal Fluid in Meningitis. Science 100: 132-133, 11 Aug. 1944.

Studies were undertaken at the Regional Hospital at Fort Bragg, N.C., to obtain further information on the most efficient mode of therapy. In 20 patients with primary or secondary syphilis given 20,000 to 40,000 units of penicillin every 3 hours from 1 to 8 days, no penicillin appeared in the spinal fluid. In six patients with meningococcemia uncomplicated by meningitis, 25,000 to 40,000 units of penicillin were given at the same interval. Twelve specimens of spinal fluid obtained 8 and 24 hours after institution of therapy and on the fifth and ninth days of treatment showed no penicillin. One patient with tuberculous meningitis showed a trace of penicillin at the 11th hour after 200,000 units of penicillin, and none at the 23d hour. Another patient with the same disease was given comparable amounts and showed no penicillin in the spinal fluid at 18 hours, and only a trace at 23 hours when the blood level was 0.4 units per cubic centimeter. Two patients with meningococcal meningitis were treated intramuscularly only. One showed a measurable amount of penicillin in the spinal fluid only at 24 hours, and in the other assays revealed none at 1½, 2½, 10, and 16 hours after treatment was begun. Both patients showed initial improvement but relapsed after 24 hours. In one, culture of the spinal fluid remained positive for meningococci. Both patients recovered promptly when sulfadiazine was administered. In seven other patients with meningococcal meningitis, penicillin was administered (intramuscularly) in large doses in the early part of their illness prior to beginning the usual therapy with sulfadiazine. The range of penicillin in the spinal fluid was from 0 to 0.5 units per cubic centimeter, 1½ to 27 hours after treatment was started. It is clear that, without intrathecal administration, penicillin may penetrate into the spinal fluid, but irregularly and in low concentrations. This work did not invalidate reported recoveries, but it indicated the hazards of modes of therapy that exclude the intrathecal route.

It was demonstrated [64] that, following the administration of 10,000 units of penicillin intrathecally, from 4 to 20 units per cubic centimeter were still present in the spinal fluid 8 hours later and from 0.08 to 0.31 units after 24 hours.

In a study [65] of comparable cases of uncomplicated meningococcal bacteremia, 18 were treated with penicillin and 12 with sulfadiazine. All patients recovered and were free of symptoms within 24 hours. Those treated with penicillin had normal temperatures at 12 hours while, in the sulfadiazine group, the temperatures remained elevated for 24 hours. The rash faded in both groups in 2 days. Penicillin was apparently more effective than sulfadiazine in rapidly controlling symptoms in this group. However, its inconstant appearance in the spinal fluid after intramuscular injection made it a less desirable mode of therapy, since bacteriostatic levels of penicillin in

[64] See footnote 61 (2), p. 266.
[65] See footnote 61 (1), p. 266.

the spinal fluid could not be depended upon to prevent meningitis, or to control early meningitis if it occurred in these cases.

In eight patients with meningococcal meningitis, alternate cases were treated either with sulfadiazine in the usual dosage, or with 25,000 to 40,000 units of penicillin every 3 hours intramuscularly and 10,000 units intrathecally daily for 3 days.[66] All patients recovered. Those treated with sulfadiazine developed normal temperatures more rapidly, became free of headache and meningeal manifestations sooner, and were out of bed earlier than those who received penicillin. One patient who received intrathecally 10,000 units of a dark-colored penicillin in 10 cc. of normal saline promptly developed extreme headache, stiffness of the neck, opisthotonos, and increasing fever associated with a rise of leukocytes in the spinal fluid from a few hundred to 50,000 within a few hours. It became necessary to stop the intrathecal penicillin and resort to sulfadiazine therapy. One other patient given the same dark-colored penicillin developed meningeal irritation of less marked grade.

In reviewing 300 fatalities due to meningococcal infection (table 36), instances of the administration of 20,000 to 25,000 units of penicillin intrathecally were noted. In one, following a large cisternal dose, hemorrhage in the medulla was found at necropsy.[67] Several instances of pleocytosis and actual hemorrhage have attended doses in excess of 10,000 units.[68]

Meningitis developed in two patients[69] while on intramuscular penicillin. One was being treated for meningococcemia and one for abdominal wounds. From the history of the first patient it is possible that meningitis already existed in spite of a normal spinal fluid.

In rare instances, penicillin was effective when sulfadiazine failed. A native of New Guinea (at Aitape) was seen at the 30th Evacuation Hospital by the author and Col. Vernon J. Erkenbeck, MC, in a moribund condition with meningococcal meningitis. He had been under treatment with massive doses of sulfadiazine for 5 days, and concentrations of sulfadiazine in blood and spinal fluid were high. In spite of this, there was extreme opisthotonos and hyperpnea, and death seemed imminent. Penicillin intrathecally and intravenously produced rapid improvement and ultimate recovery.

Since World War II, it has been shown that satisfactory cerebrospinal fluid levels of penicillin can be attained by the intramuscular route alone if enough penicillin is given. Dowling and his coworkers[70] found that 1 million units of aqueous penicillin intramuscularly every 2 hours resulted in adequate concentrations in the cerebrospinal fluid.

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66 See footnote 52 (2), p. 265.

67 See footnote 18, p. 251.

68 Annual Report, Professional Service Division, Medical Consultation Service, Office of the Chief Surgeon, Headquarters, European Theater of Operations, U.S. Army, 30 Dec. 1944, p. 13.

69 (1) See footnote 61 (5), p. 266. (2) Personal communication, W. M. M. Kirby, to the author.

70 Dowling, H. F., Sweet, L. K., Hirsh, H. L., and Lepper, M. H.: Specific Therapy of Bacterial Infections of the Central Nervous System. J.A.M.A. 139: 755-758, 19 Mar. 1949.

It becomes clear that sulfadiazine has proved to be the drug of choice in the mild or average instance of meningococcal infection. Penicillin should not be used as a routine measure. It should be given in massive dosage in conjunction with sulfadiazine in fulminating bacteremia or meningitis, and to replace it when intolerance to, or complications from, sulfadiazine develop. When improvement is not noted after 36 hours of treatment with sulfadiazine, massive parenteral penicillin therapy should be instituted without discontinuing sulfadiazine.

Therapy With Other Drugs

Certain new antibiotics that have become available since World War II are highly effective in the treatment of both bacteremia and meningitis. Aureomycin (chlortetracycline),[71] chloramphenicol,[72] and Terramycin (oxytetracycline)[73] have been used successfully in the treatment of small groups of patients. Should a patient demonstrate clear-cut evidence of sensitivity to the sulfonamides and penicillin, one of these other drugs can be used with confidence.

Adjuvant Therapy

Fluid balance.—Patients admitted with meningitis, or severely ill with bacteremia, are almost invariably dehydrated, so that careful attention to fluid balance is necessary for its own sake as well as to prevent the renal complications of sulfonamide therapy. Urine flow should not be less than 1,200 cc. per day. Attention to this detail of therapy was often painfully learned by medical officers when gross hematuria or oliguria developed during administration of sulfadiazine. It was soon found that the use of sodium sulfadiazine in 5 percent solution, as suggested in Circular Letter No. 170, was fraught with danger unless a large amount of fluid had preceded treatment. When the patient's condition permits slight delay, Ochs' recommendation[74] of 2,000 cc. of ⅙ molar sodium lactate prior to sulfadiazine may be wise. He also advocated using the same quantity of this solution following the drug and the maintenance of an alkaline urine. However, renal complications were rare when the initial dose of sodium sulfadiazine was administered in 1,000 cc. of isotonic sodium chloride or the same volume of ⅙ molar sodium lactate. In some hospitals, the major portion of the intake of fluid was administered to comatose patients by Levin tube and in others by a parenteral route. The latter is preferable when there is vomiting.

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[71] Conn, Howard F. (editor): Current Therapy. Philadelphia: W. B. Saunders Co., 1951, p. 19.

[72] McCrumb, F. R., Jr., Hall, H. E., Merideth, A. M., Deane, G. E., Minor, J. V., and Woodward, T. E.: Chloramphenicol in the Treatment of Meningococcal Meningitis. Am. J. Med. 10: 696–703, June 1951.

[73] Hoyne, A. L., and Riff, E. R.: Terramycin Therapy for Meningitis; A Report of Fourteen Recoveries Without Other Medication. J. Pediat. 39: 151–154, August 1951.

[74] See footnote 43 (1), p. 262.

Sedation.—Restlessness is common and when mild can be disregarded or allayed by simple sedatives, such as the barbiturates. Great restlessness and almost maniacal delirium occur frequently with meningitis, often making lumbar puncture or intravenous treatments difficult or impossible. Paraldehyde, 16 cc., proved the most effective sedative. Intravenous barbiturates are occasionally necessary, though undesirable. Morphine, though considered hazardous by some because of its depressant effect on respiration, is at times essential. Extreme restlessness and even delirium can often be relieved by lumbar puncture with the reduction of pressure of the spinal fluid. Catheterization with relief of bladder distention often quiets a restless, thrashing patient who is hard to keep in bed. It has been noted that the delirium is frequently a resistive one, so that attempts to restrain the patient's movements result in a heightening of delirium. Freedom to thrash about in bed for a few minutes without restraint is often followed by quiet and relaxation. In fulminating bacteremia, morphine appears to be the most effective drug for restlessness and is indicated if shock supervenes.

Lumbar puncture.—Initial diagnosis may be the only occasion for the use of this procedure in patients who show prompt and continued improvement following treatment. As a therapeutic procedure for reduction of intracranial pressure, lumbar puncture is of great importance when headache is excessive, restlessness intractable, coma deepening, and hyperpnea, Biot's breathing, or other respiratory abnormalities are marked. Striking improvement has been noted in patients following reduction in intracranial pressure.

Complete recovery with return to full duty after an average hospitalization for 1 month and a similar period on sick furlough or reconditioning has been usual. Data as to actual days lost are not available. In mild and uncomplicated bacteremia, many soldiers have been returned to full duty within 2 weeks from onset.

Preliminary tabulations of individual medical records, during 1942–45, indicate that 105 U.S. Army personnel were separated for disability due to meningococcal infection.

PATHOLOGICAL FINDINGS

The vast amount of pathological material available at the Armed Forces Institute of Pathology is being carefully studied by the medical officers assigned there. The major lesions disclosed at autopsy in those patients who died of meningitis were inflammatory changes in the leptomeninges of the brain and cord, usually without evidence of organization of exudate. True encephalitis was present in relatively few cases (p. 257). The pathological findings in patients with meningitis who died early were comparable with those who died of bacteremia.

Of the 156 patients who died from fulminating bacteremia (table 36), 126 showed hemorrhage in the adrenal glands ranging from mild extravasa-

tions to the conversion of both glands into sacs of blood. There was no evidence of meningitis in 74 of these 156 patients and in 64 others the meningeal inflammation was minimal. Pulmonary edema was striking in almost all and gross hemorrhage into the lung was not unusual. There were small effusions into one or both pleural cavities in about half of the patients. Widespread focal hemorrhages were scattered over the serous surfaces in most cases and sometimes involved the myocardium. Interstitial myocarditis, occasionally severe but usually of mild focal character, occurred in 28 of the 126 patients with adrenal hemorrhage. Renal changes indicative of shock were observed in 6 of 26 patients analyzed by Thomas.[75] As has been noted (p. 263), in only 3 of the 300 patients who died of meningococcal infection was death the result of renal lesions due to sulfonamides.

TREATMENT OF MENINGOCOCCAL INFECTIONS

It seems worthwhile to outline briefly recommendations for treatment based on the published reports and the experience of many medical officers with about 14,000 patients ill with meningococcal infection during World War II, and on advances in therapy since the war ended.

Acute or chronic bacteremia.—Sulfadiazine, 4.0 gm., should be given by mouth and be followed by 1 gm. every 4 hours until fever, symptoms, and other manifestations of infection have been absent for at least 48 hours. When there is vomiting, comparable amounts of sodium sulfadiazine dissolved in a liter of normal saline solution should be administered intravenously. These dosages are usually sufficient to maintain a concentration in blood from 5 to 11 mg. per 100 cc. of plasma, and as a rule prevent the development of fulminating bacteremia or meningitis.

Fulminating bacteremia with peripheral circulatory failure.—This is a major medical emergency requiring immediate action and continued, constant observation by resourceful physicians and nurses. Even though meningitis is present or suspected, it is of quite secondary importance, and the patient should not be subjected to the strain of lumbar puncture.

An hourly chart of pulse, respiration, temperature, and blood pressure is begun. The patient is placed in the shock position. Oxygen is administered continuously to combat cyanosis. External warmth is applied. An infusion of sodium sulfadiazine, 0.1 gm. per kilogram of body weight dissolved in 1,000 cc. of normal saline solution, is begun in an antecubital vein of one arm; in the other arm, an infusion of 500 cc. of 10 percent dextrose in water is begun; 500,000 units of penicillin dissolved in 20 cc. of normal saline solution are injected into the tubing and then 100 cc. of aqueous adrenocortical extract. This is followed by 500 cc. of plasma or blood, if it appears necessary. Meanwhile, the following intramuscular injections are given: (1) Cortisone, 200 mg. divided into four 50 mg. doses injected into

[75] See footnote 14 (2), p. 244.

four separate sites, and (2) penicillin, 1 million units divided into two 500,000-unit doses injected into two separate sites. If the systolic blood pressure is 80 mm. of mercury or less, a 4-cc. ampule of *l*-norepinephrine (levofed bitartrate, each cubic centimeter containing 1 mg. of levofed base) should be added to the flask of 10 percent glucose and given at a rate necessary to maintain adequate blood pressure. This is usually about 2 to 4 μg. per minute.

Further therapy may include: (1) Plasma, or 25 gm. of concentrated human albumin administered in 5 percent solution, if indicated for shock; (2) sodium sulfadiazine, 0.05 gm. per kilogram of body weight every 4 hours intravenously until the drug (approximately 1 to 1.5 gm. every 4 hours) is tolerated by the oral route; (3) penicillin, 1 million units every 2 hours intramuscularly; (4) cortisone, 50 mg. intramuscularly every 6 hours for the first 2 days and 25 mg. every 6 hours for the next 3 days; thereafter, the dose should be gradually discontinued over the course of a week; and (5) small quantities of ginger ale or sweetened fruit juice, orally, as soon as possible amounting to 3,000 cc. of fluids or more daily.

The dosage of sulfadiazine should be guided by frequent determinations of drug level in the blood, 15 to 20 mg. per 100 cc. being the optimum range Full chemotherapy should be continued for at least 4 days after the patient has recovered from the acute phase of his disease, counted from the first day of normal temperature.

After the first day, no more than 1,000 cc. of normal saline need be given daily intravenously. Should pulmonary, sacral, or peripheral edema appear, however, the quantity of normal saline solution should be markedly reduced. If marked pulmonary edema develops, 1 to 3 units of plasma or 25 to 50 gm. of concentrated human albumin may be administered slowly. Positive pressure oxygen may be helpful.

If the patient is failing, hypoglycemia and hypopotassemia should be considered. The appropriate blood determinations should be made, and their abnormalities corrected. An electrocardiogram might show evidence of potassium deficiency.

In those patients with fulminating bacteremia whose manifestations are not those of shock, the use of plasma, norepinephrine, oxygen, and adrenocortical compounds should be omitted.

A count of circulating eosinophils should be performed to assist in differentiation of the Waterhouse-Friderichsen syndrome from fulminating sepsis without adrenal insufficiency; the former may show more, and the latter less, than 50 cells per cubic millimeter. Cortisone dosage should be adequate to maintain the number of eosinophils at 15 per cubic millimeter or less.

Meningitis.—The potential seriousness of this condition is such that, regardless of its severity, all patients should receive a liter of saline containing sodium sulfadiazine intravenously—6 gm. for a heavyweight, 5 gm. for

a mediumweight, and 4 gm. for a lightweight adult. It is wise to administer half the original dose parenterally 4 hours later, but, in conscious and cooperative patients who are not vomiting, the oral route may be used at this time. If, following this, continued parenteral therapy is needed, 2 gm. of sulfadiazine dissolved in saline should be injected intravenously or subcutaneously every 8 hours. In comatose patients, the drug may be administered by stomach tube. Sulfadiazine, in doses of 1 to 1.5 gm. orally every 4 hours, will usually maintain the concentration in blood around 8 mg. and concentration in the spinal fluid around 6 mg. per 100 cc. A concentration in blood of 6 to 10 mg. is adequate. In fulminating cases, the dosage should be adjusted to maintain the concentration in the blood between 15 and 20 mg. per 100 milliliter. In the gravely sick cases, penicillin should also be used, in the doses just mentioned. If the patient is known to be sensitive to, or develops complications of, sulfonamide treatment, penicillin in massive dosage (1 million units every 2 hours) should replace it. If sensitivity to both of these agents should be present, chloramphenicol, Aureomycin, and Terramycin are effective drugs.

DISCUSSION

The experiences of medical officers who have treated meningococcal infection during the Second World War have clarified and extended knowledge of the various forms which this infection may assume. These observations amply confirmed the opinion of Herrick and others in the World War I epidemic that the disease begins as a bacteremia and, if not prevented by spontaneous resistance or therapy, involves the meninges, skin, and other organs, or it may be fatal in the bacteremic form.

The major contribution has been the development of a tried therapeutic plan, which has reduced the case fatality to 4 percent in contrast to about 31 percent in World War I (table 34). In the Zone of Interior, where no problem of evacuation existed, the case fatality was 3.9 percent compared to 4.5 percent for oversea areas. The ratios for the continental United States in 1944 and 1945 were, respectively, 2.9 and 4.9 percent, based on 2,577 and 815 cases. It is not probable that with our present therapeutic tools mortality can be further significantly reduced, unless some means can be found which will enable the physician to recognize incipient meningococcal bacteremia during the phase of prodromal respiratory symptoms.

CHAPTER X

Cutaneous and Other Aspects of Diphtheria

Averill A. Liebow, M.D., and John H. Bumstead, M.D.

Diphtheria was a new and serious problem to the U.S. Army during the Second World War. Combat in the tropics again proved to be particularly favorable for the spread of this disease, especially the cutaneous form. During the First World War, the British recognized the diphtheritic nature of the desert sores that were so prevalent among the troops in Egypt and Palestine. In World War II, lesions of the same nature were common during the North African campaign over similar terrain. During 1943 and 1944, cutaneous diphtheria on a large scale became apparent among troops in the Pacific. Hitherto, it had not been reported from that area, and it was not until *Corynebacterium diphtheriae* was found in such lesions known as tropical ulcer, ecthyma, and jungle rot that their etiology was determined. These lesions were of epidemiological importance because they were a prolific source of pharyngeal and nasal diphtheria among the soldiers and to those with whom they came in contact. It was found that an enormous reservoir of diphtheria—in the cutaneous form resembling that seen in soldiers—existed among natives in the Pacific, particularly among the children. The lesions of childhood probably accounted for the immunization of the natives early in life. It seemed that the conditions of combat reduced American soldiers to the epidemiological conditions prevailing among the natives.

Studies of the lesions of soldiers and of natives in the tropics revealed the presence of a hitherto unknown hemolytic corynebacterium, which could easily be confused either with *C. diphtheriae* on Löffler's medium or with the beta hemolytic streptococcus on blood-agar plates.

Several groups of investigators seized the opportunity to study the effectiveness of penicillin in the treatment of the numerous carriers and clinical cases of diphtheria that were available in some hospitals.

Part I. General Aspects of the Military Problem

INCIDENCE

Preliminary statistical data on the incidence (total cases) of diphtheria in the U.S. Army for the years 1942–45 by area, based on sample tabulations of individual medical records, are presented in table 40. During 1942 through 1945, 619 cases of diphtheria were reported in the Army in the continental United States and 5,105 additional cases from the Army overseas. Among the oversea theaters in 1945, the year of highest number of cases, the European Theater of Operations, U.S. Army, had the highest rate, with the

North African and Mediterranean Theater of Operations, U.S. Army, second, and the combined Pacific areas, third.

Deaths due to diphtheria, during World War II, totaled 125 (table 41). Of the total, 115 occurred in the Army overseas. Mortality was greater in 1945 for the Army as a whole, with 67 deaths occurring in the European theater alone.

TABLE 40.—*Incidence of diphtheria in the U.S. Army, by area and year, 1942–45*

[Preliminary data based on sample tabulations of individual medical records]
[Rate expressed as number of cases per annum per 1,000 average strength]

Area	1942–45		1942		1943		1944		1945	
	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate
Continental United States	619	0.04	67	0.03	205	0.04	152	0.04	195	0.07
Overseas:										
Europe	2,557	0.58	27	0.33	45	0.17	245	0.15	2,240	0.94
Mediterranean [1]	1,087	.73	2	.09	197	.43	628	.97	260	.73
Middle East	45	.31	1	.17	23	.43	11	.24	10	.24
China-Burma-India	208	.47	8	.91	15	.38	155	.92	30	.14
Southwest Pacific	615	.33	3	.04	7	.04	100	.19	505	.49
Central and South Pacific	519	.41	4	.03	69	.24	266	.61	180	.48
North America [2]	19	.04	2	.02	3	.02	14	.11	----------	0
Latin America	23	.06	5	.05	2	.02	1	.01	15	.21
Total overseas [3]	5,105	0.48	55	0.09	364	0.22	1,426	0.37	3,260	0.70
Total Army	5,724	0.22	122	0.04	569	0.08	1,578	0.20	3,455	0.46

[1] Includes North Africa.
[2] Includes Alaska and Iceland.
[3] Includes admissions on transports.

Evidence is presented (p. 315) that cutaneous diphtheria probably played an important role in the dissemination of all forms of the disease, although relatively few cases were diagnosed and reported officially. For example, the incidence of cutaneous diphtheria in the total Army in 1944 and 1945, based on sample tabulations of individual medical records, totaled 485 (table 42). The majority of cases occurred in the combined Pacific areas and in the China-Burma-India theater.

Among the British in the African desert, the rate for all forms of diphtheria was 4 to 5 per 1,000 per annum.[1] A comparison of British and American incidence of diphtheria in the Mediterranean theater during December 1943 and January and February 1944 follows:

	British	*American*
December 1943	558	64
January 1944	490	42
February 1944	302	33

[1] Proceedings of the Conference of Army Physicians, Central Mediterranean Forces, Held at the Institute Superiore di Sanita, Viale Regina Marguerita, Rome, 29 Jan. to 3 Feb. 1945, pp. 101–118.

TABLE 41.—*Deaths due to diphtheria in the U.S. Army, by area of admission and year of death, 1942–45*

[Preliminary data based on tabulations of individual medical records]

[Rate expressed as number of deaths per annum per 100,000 average strength]

Area	1942–45		1942		1943		1944		1945	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Continental United States	10	0.07	.....	0.00	2	0.04	2	0.05	6	0.20
Overseas:										
Europe	72	1.64	.....	0	.....	0	5	0.30	67	2.82
North Africa	11	.74	.....	0	4	.88	3	.46	4	1.13
Middle East	3	2.05	.....	0	2	3.77	1	2.16	.....	0
China-Burma-India	3	.68	1	11.43	.....	0	2	1.19	.....	0
Pacific [1]	21	.68	.....	0	2	.42	8	.82	11	.78
North America	2	.41	.....	0	.....	0	1	.77	1	1.47
Latin America	.....	0	.....	0	.....	0	.....	0	.....	0
Total overseas [2]	115	1.07	1	0.17	8	0.47	20	0.52	86	1.85
Total Army	125	0.49	1	0.03	10	0.15	22	0.28	92	1.21

[1] Total Pacific Area (Southwest, Central, and South Pacific).

[2] Includes 3 deaths on transports in 1945.

TABLE 42.—*Incidence of cutaneous diphtheria in the U.S. Army, by area and year, 1944–45*

[Preliminary data based on sample tabulations of individual medical records]

[Rate expressed as number of cases per annum per 1,000 average strength]

Area	1944–45		1944		1945	
	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate
Continental United States	15	0.00	5	0.00	10	0.00
Overseas:						
Europe	45	0.01	.....	0	45	0.02
Mediterranean [1]	6	.01	1	.00	5	.01
Middle East	.....	0	.....	0	.....	0
China-Burma-India	120	.31	110	.65	10	.05
Southwest Pacific	205	.13	30	.06	175	.17
Central and South Pacific	89	.11	54	.12	35	.09
North America [2]	.....	0	.....	0	.....	0
Latin America	.....	0	.....	0	.....	0
Total overseas [3]	470	0.06	195	0.05	275	0.06
Total Army	485	0.03	200	0.03	285	0.04

[1] Includes North Africa.

[2] Includes Alaska and Iceland.

[3] Includes admissions on transports.

NOTE.—Absolute zero is indicated by zero in the units column; 0.00 indicates a rate of more than zero but less than 0.005.

It must be stated, however, that the Americans required laboratory confirmation of diagnosis, whereas the British did not. The rate among German prisoners of war was far in excess of that of American soldiers. Local epidemics were reported in German prisoner-of-war camps in the United States.[2] In some cases, cutaneous diphtheria was described, and tropical ulcers were reported to be numerous among the prisoners. At the same time, diphtheria increased steadily among Army troops in the continental United States.

After the occupation of Germany, the incidence of nasopharyngeal diphtheria increased tremendously, probably through association of soldiers with the civilian population among whom, during the war years, diphtheria had become a major problem. Circular Letter No. 69, Office of the Theater Chief Surgeon, Headquarters, Theater Service Forces, European Theater, issued on 28 September 1945, summarized for medical officers the general principles to be followed in the diagnosis, treatment, and control of diphtheria. In addition, the December 1945 and January 1946 issues of the *Medical Bulletin* from the Office of the Theater Chief Surgeon contained a series of articles on diphtheria written by medical officers in the theater.

During the calendar year 1945, 2,240 cases of diphtheria occurred among American troops in Europe with 67 deaths (tables 40 and 41). The incidence in December 1945 was approximately 2.8 per 1,000. During the early months of 1946, from 30 to 50 cases were being diagnosed each week with 1 or more deaths.

IMMUNIZATION

The policy at first was not to immunize young adults routinely against diphtheria because moderate to severe reactions would occur in an appreciable number of cases, although studies were made of the incidence of Schick-positive reactors among U.S. Army troops and small diphtheria-immunization programs were conducted.[3] Late in 1945, as the incidence of diphtheria increased among U.S. troops in the European theater, only immune personnel were assigned to the army of occupation on the Continent. U.S. Army civilian employees, their dependents, and dependents of military personnel destined to join the occupation army in the European theater were immunized.

[2] (1) Fleck, S., Kellam, J. W., and Klippen, A. J.: Diphtheria Among German Prisoners of War. Bull. U.S. Army M. Dept. No. 74, pp. 80-89, March 1944. (2) Monthly Progress Report, Army Service Forces, War Department, 30 Nov. 1943, Section 7: Health, p. 22.

[3] For a more detailed discussion of the diphtheria-immunization program during World War II, the reader is referred to the following two sources: (1) Long, Arthur P.: The Army Immunization Program. *In* Medical Department, United States Army. Preventive Medicine in World War II. Volume III. Personal Health Measures and Immunization. Washington: U.S. Government Printing Office, 1955, pp. 271-341. (2) McGuinness, Alma C.: Diphtheria. *In* Medical Department, United States Army. Preventive Medicine in World War II. Volume IV. Communicable Diseases Transmitted Chiefly Through Respiratory and Alimentary Tracts. Washington: U.S. Government Printing Office, 1958, pp. 167-189.- J. B. C., Jr.

Accordingly, on 12 January 1946, the Office of the Theater Chief Surgeon, European Theater,[4] directed all major commands to institute an immunization program for (1) all medical department, hospital, and dispensary personnel, (2) all personnel whose duties brought them into frequent and intimate contact in camps or enclosures with prisoners of war, displaced persons, internees, or German civilians, and (3) all units of battalion strength or smaller showing two cases in any one week. It was decided to dispense with Schick testing at that time.

In May 1946, the rule was changed, and all military personnel going overseas who were shown to be susceptible to diphtheria by the Schick test were ordered to be immunized.

Part II. Tropical Ulcers and Diphtheria

SOURCES AND DISSEMINATION OF INFORMATION

The presence of *C. diphtheriae* in skin lesions, particularly ulcers, was reported by widely separated groups of observers in the South and Southwest Pacific Areas and in Burma during World War II. However, in Saffron's 1944 review of the literature on cutaneous diphtheria no mention was made of the incidence in these areas.[5]

Cutaneous diphtheria was recognized among American forces in the Mediterranean theater but was the subject of only one brief general report.[6] More interest was displayed by the British, among whom the incidence of diphtheria was generally higher.[7]

South Pacific.[8]—The observations in the South Pacific Area were made chiefly on members of the 25th and 43d Infantry Divisions, as they were evacuated from combat in the Solomon Islands, and on troops of the 27th Infantry Division, following their evacuation to Espíritu Santo in the New Hebrides after the Battle of Saipan. The first of a series of reports from the 39th General Hospital, Auckland, New Zealand, appeared in September 1943. The information was soon disseminated throughout the area in Medical Circular Letters Nos. 5 and 14, dated 20 October 1943 and 5 January 1944, respectively, Headquarters, U.S. Army Forces, South Pacific Area.

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[4] Medical Bulletin No. 2, Office of the Theater Chief Surgeon, Headquarters, Theater Service Forces, European Theater, January 1946, pp. 1-7.

[5] Saffron, M. H.: Cutaneous Diphtheria as a Military Problem; A Review of the Literature, With Report of a Case. Arch. Dermat. & Syph. 51: 337-340, May 1945.

[6] Medical Bulletin No. 19, Office of the Chief Surgeon, Headquarters, European Theater of Operations, 1 May 1944, pp. 27-29.

[7] (1) See footnote 1. p. 276. (2) Hunt, T. C.: Medical Experiences in North Africa, 1943-44. Brit. M.J. 2: 495-498, 14 Oct. 1944. (3) Diphtheria in Campaigns. British M. Bull. No. 36, pp. 1-2, June 1944. (4) MacGibbon, T. A.: Diphtheria in the Middle East; Some Observations on 71 Cases. Edinburgh M.J. 50: 617-625, October 1943. (5) Williams, H. C. M.: Cutaneous and Conjunctival Diphtheria; Series of Cases. Brit. M.J. 2: 416-417. 2 Oct. 1943.

[8] Unless otherwise indicated, the material presented in this chapter on tropical ulcers and cutaneous diphtheria in the South Pacific is taken from Liebow, A. A., MacLean, P. D., Bumstead, J. H., and Welt, L. G.: Tropical Ulcers and Cutaneous Diphtheria. Arch. Int. Med. 78: 255-295, September 1946.

Similar material on diphtheria was made available in February 1944 by newsletter from U.S. Navy headquarters for malarial and epidemic control in the South Pacific Area. In addition, there were the evangelical efforts of the medical consultant, Col. Benjamin M. Baker, MC, who did much to make the staffs of the various hospitals conscious of the diphtheria problem. The final report totaled 174 cases of cutaneous diphtheria and 94 cases of noncutaneous diphtheria, in all of which *C. diphtheriae* had been demonstrated.

The following tabulation is based on a study of patients from the Solomon Islands campaign at the 39th General Hospital from 7 February 1943 to 1 July 1944, inclusive, and on cases of diphtheria from the 27th Infantry Division during their stay at the rest area on Espíritu Santo:

Type of cases	*Number of cases*	*Proportion of strains toxigenic*
Cutaneous diptheria	174	145:173
Throat cases	64	60:62
Nose cases	5	5:5
Nose and throat cases	1	1:1
Carriers	24	12:23

The clinical observations on cases in the Saipan group admitted to the 122d Station Hospital on Espíritu Santo were also reported separately from this hospital.[9] On Fiji, 35 cases of nasopharyngeal diptheria were found in the 164th Infantry of the Americal Division following the Guadalcanal campaign. Diphtheria among marines in process of evacuation from Guadalcanal has been described by Norris and his coworkers.[10] The laboratory work on diphtheria in the various hospitals in the South Pacific has been reviewed by Murray.[11]

During the early phases of the South Pacific study, from March to September 1943, intensive parasitological and bacteriological studies were made, including anaerobic cultures, dark-field examinations, potassium hydroxide smears, cultures for fungi, and Giemsa stains for *Leishmania.* Cutaneous lesions were searched with care for *Leishmania* in cases from the Solomon Islands and Saipan, but neither protozoa nor spirochetes were found, and such fungi as *Monilia* and *Epidermophyton* were rarely encountered. When the frequency of *C. diphtheriae* became apparent, a special procedure was employed to investigate the epidemiology and pathogenesis of lesions associated with this micro-organism, and bacteriological methods were simplified to facilitate its detection. A standard clinical record form was designed, which emphasized such factors as previous diphtheria, immunization, former Schick tests, history of sore throat, and evidences of neurological damage.

[9] Stern, R. L., and Grynkewich, S. E.: Diphtheria Epidemic in Adults in the Tropics. Bull. U.S. Army M. Dept. 5(5): 562–569, May 1946.

[10] Norris, R. F., Kern, R. A., Schenck, H. P., and Silcox, L. E.: Diphtheria in the Tropics; A Report of 18 Cases on a United States Naval Hospital Ship. U.S. Nav. M. Bull. 42: 518–524, March 1944.

[11] Murray, R.: Laboratory Service—South Pacific Area. [Official record.]

Routine nose and throat cultures were taken, and Schick tests were made in all instances where nasal or pharyngeal diphtheria did not make immediate treatment imperative. Before a patient was discharged from a hospital, another physical examination with emphasis on the neurological aspects was performed.

Burma.—In the Burma portion of the India-Burma theater, 141 cutaneous lesions were found, chiefly in soldiers from the Myitkyina combat area. They were reported from the 20th General Hospital, Ledo, Assam, in September 1944, by Livingood and his coworkers, who had given them careful study.[12] In 21 percent of these 141 patients, it was possible to demonstrate toxigenic *C. diphtheriae*. There was, however, a high incidence of complications among those lesions from which *C. diphtheriae* was not isolated, but since they were morphologically identical with those harboring the microorganisms, the diagnosis of cutaneous diphtheria seemed reasonable. Only eight cases of nasopharyngeal diphtheria were diagnosed in the interval during which most of these cutaneous cases were observed—September to December 1944. Particular attention was paid to the complications of the disease as well as to morphology of the characteristic lesions and their treatment, and a valuable followup study was made, which furnished an estimate of the cost to the Army in man-days.[13]

Reports from the 69th General Hospital, Ledo, Assam, in October 1944 and January 1945 [14] referred to 70 patients. All throat cultures in this series were negative, and no clinical cases of nasopharyngeal diphtheria were diagnosed.

It is interesting to note that the British in the India-Burma theater at the same time were seeing a number of cases of cutaneous diphtheria, some with neurological complications.[15]

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[12] (1) Cutaneous Diphtheria, 20th General Hospital, 20 April 1945. *In* Blumgart, Herrman L., and Pike, George M.: History of Internal Medicine in India-Burma Theater, inclosure 11 thereto. [Official record.] (2) Letter, Maj. Clarence S. Livingood, MC, Office of Chief of Dermatology and Syphilology, 20th General Hospital, to Commanding Officer, 20th General Hospital, 15 Sept. 1944, subject: Cutaneous Diphtheria. (3) Letter, Maj. Clarence S. Livingood, MC, Office of Chief of Section of Dermatology and Syphilology, 20th General Hospital, to Commanding Officer, 20th General Hospital, 9 Oct. 1944, subject: Cutaneous Diphtheria. (4) Letter, Maj. Clarence S. Livingood, MC, Chief, Section of Dermatology and Syphilology, 20th General Hospital, India-Burma Theater, to Commanding Officer, 20th General Hospital, 25 Jan. 1945, subject: Cutaneous Diphtheria. (5) Letter, Lt. Col. Francis C. Wood, MC, Chief of Medical Service, 20th General Hospital, to Commanding Officer, 20th General Hospital, 15 Sept. 1944, subject: Cutaneous Diphtheria. (6) Letter, Maj. Herbert S. Gaskill, MC, Chief, Neuropsychiatric Section, 20th General Hospital, India-Burma Theater, to Commanding Officer, 20th General Hospital, 18 Mar. 1945, subject: Preliminary Report on the Neuritis Complicating Cutaneous Diphtheria.

[13] Letter, Capt. Daniel J. Perry, MC, Assistant Chief, Dermatology and Syphilology Section, 20th General Hospital, to Consultant in Dermatology, Office of the Surgeon General, 28 Aug. 1945, subject: Follow-Up Studies of a Group of 140 Cases of Cutaneous Diphtheria.

[14] (1) Letter, Capt. Harvey Blank, MC, Chief, Section of Dermatology and Syphilology, 69th General Hospital, India-Burma Theater, to Commanding Officer, 69th General Hospital, 31 Jan. 1945, subject: Analysis of 40 Additional Cases of Cutaneous Diphtheria. (2) Letter, Capt. Harvey Blank, MC, Chief, Section of Dermatology and Syphilology, 69th General Hospital, Advance Section 3, India-Burma Theater, to Commanding Officer, 69th General Hospital, 1 Apr. 1945, subject: Report of Cutaneous Diphtheria Among the Detachment of a General Hospital.

[15] Blumgart, Herrman L., and Pike, George M.: History of Internal Medicine in India-Burma Theater. [Official record.]

Southwest Pacific.—The group at the 9th General Hospital on Biak [16] observed a total of 210 cases of diphtheria between 1 November 1944 and 1 March 1945. There were 102 cases of dermatitis from which *C. diphtheriae* was isolated. Of the 31 recovered strains tested, 19 were virulent. There were also 60 other cases with wounds, burns, otitis media, otitis externa, and other such lesions, and 48 nasopharyngeal infections from which the *C. diphtheriae* was isolated. The patients in this group were from nine widely scattered bases in the Southwest Pacific Area, New Guinea, the Netherlands East Indies, and the Philippine Islands. On Biak, where the studies were conducted, 112 patients were from 22 different organizations.

Quarterly reports from several hospitals in the Southwest Pacific Area, among them the 54th General Hospital on Biak and the 105th General Hospital in Hollandia, New Guinea, indicated early in 1945 that diphtheria was under surveillance. During a 3-month period at the 13th General Hospital, Finschhafen, northeast New Guinea, 26 cases of nasopharyngeal diphtheria were seen together with 25 individuals who had cutaneous lesions from which *C. diphtheriae* was cultured. They were usually virulent micro-organisms of the *mitis* type. Technical Bulletin No. 17, Office of the Chief Surgeon, Headquarters, U.S. Army Forces in the Far East, dated 23 October 1944, called to the attention of all medical officers the increase in the number of reported cases of clinical diphtheria in the area and directed that measures be instituted to prevent the spread of the disease.

Zone of Interior.—After prevalence of the condition was recognized, the patients with cutaneous lesions received thorough study in several large centers in the United States. At the Moore General Hospital, Swannanoa, N.C.,[17] a skin isolation ward was established to which there were 228 admissions between 1 March and 3 October 1945. Cultures of ulcerated lesions in the skin were positive for corynebacteria in 107, 18 of which proved to be toxigenic. At the Harmon General Hospital, Longview, Tex.,[18] a survey was made of 385 admissions; most of the patients in the survey were from the Pacific areas. Seventy persons were proved to have *C. diphtheriae* either in the nose or throat or in cutaneous lesions. Fifty-eight of these strains of the micro-organism were virulent, but 12 were toxigenic *C. diphtheriae*. This represented an incidence of 3.1 percent in the population of the hospital at the time of admission. Fifty-six of these patients had tropical ulcers or ulcerated dermatitides. In 8 of these, *C. diphtheriae* was found to be toxigenic and in 30, atoxic. At the Baxter General Hospital, Spokane,

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[16] Oppel, T. W., Smith, J. J., Montanaro, A., and Tompsett, R. R.: Clinical Features of Diphtheria in the Tropics. [Official record.]

[17] Bronson, L. M.: Memorandum on Cutaneous Diphtheria at Moore General Hospital. [Official record.]

[18] (1) Denhoff, E., and Kolodny, M. H.: Studies on Cutaneous Diphtheria and Tropical Ulcers. Arch. Dermat. & Syph. 55: 360-368, March 1947. (2) Denhoff, E., Kolodny, M. H., Daniels, W. B., and Mitchell, L. P.: Plan to Control Diphtheria in an Army General Hospital. Bull. U.S. Army M. Dept. 6: 59-60, July 1946.

Wash.,[19] between 1 December 1944 and 15 February 1945, there were 62 healed or active cases of cutaneous diphtheria, of which polyneuritis developed in 11. At the Letterman General Hospital, San Francisco, Calif.,[20] diphtheria in medical personnel attending patients on the dermatology wards again proved a problem, until the diphtheritic nature of many of the lesions encountered on these wards was recognized. The localized outbreak was studied in this hospital and will be discussed later.

Diphtheria, particularly of the cutaneous variety, was discussed in detail at the Ninth Service Command Conference on Internal Medicine held at Letterman General Hospital on 7 and 8 November 1945.

Policies.—In recognition of the increasing importance of the problem of diphtheria during World War II, information, as it became available, was disseminated by the highest echelon. The diphtheritic nature of certain types of tropical ulcers in the Pacific was first given wide publicity in the May 1944 issue of the *Bulletin of the U.S. Army Medical Department.* Following a tour of inspection of the Pacific area in October 1944 by Col. Francis R. Dieuaide, MC, Chief, Tropical Disease Treatment Branch, Medical Consultants Division, Office of the Surgeon General, War Department Technical Bulletin (TB MED) 143, entitled "Cutaneous Diphtheria" was issued in February 1945. This bulletin summarized the reports from various tropical areas, gave directions concerning diagnosis and treatment, and emphasized the epidemiological significance of the disease. Similar material on the recognition and treatment of cutaneous diphtheria was published in the March 1945 issue of the *Bulletin.* A special circular on management of patients with cutaneous diphtheria was prepared by the Medical Consultants Division, Office of the Surgeon General, and was issued to service command medical consultants on 3 August 1945.

The many cases of polyneuritis that had been reported from the Mediterranean theater,[21] the South Pacific, Burma,[22] and elsewhere, attracted the interest of the Army Epidemiological Board (Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army), which established an investigative commission composed of Dr. George D. Gammon and Maj. (later Lt. Col.) Emanuel B. Schoenbach, MC. The commission arrived in Merano, Italy, on 31 May 1945 and devoted its attention to the many cases among the German prisoners of war, since cases among U.S. soldiers were no longer available in large numbers. A preliminary report of 42 cases considered diphtheritic polyneuritis and of 28 others was submitted in August 1945.[23]

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[19] Sampson, J. J.: Late Neuronitis Following Proved and Suspected Cutaneous, Faucial and Wound Diphtheria. Am. J.M. Sc. 212: 432-448, October 1946.

[20] Letter, Maj. Frank R. Day, PhC, Adjutant, Letterman General Hospital, San Francisco, Calif., to Office of the Surgeon General, 20 Oct. 1944, subject: Reported Cases of Diphtheria at Letterman General Hospital.

[21] See footnote 1, p. 276.

[22] See footnote 12 (6), p. 281.

[23] Gammon, G. D., and Schoenbach, E. B.: Preliminary Report on Investigation of Polyneuritis in the Mediterranean Theater of Operations, U.S. Army, 20 Aug. 1945. [Official record.]

MORPHOLOGY

Typical lesions.—The characteristic lesion from which *C. diphtheriae* was demonstrated in highest incidence was rounded with angular irregularities, deep and punched out, but did not as a rule extend far into the subcutaneous tissue. In the South Pacific, 84.1 percent of lesions harboring *C. diphtheriae* had this appearance. They were similar to lesions of cutaneous diphtheria seen in temperate zones, to the desert or veldt sores of North Africa and Palestine, to the "Garigha" of northern India, and to the lesions seen among the Melanesians and Tonkinese in the New Hebrides, and the Chamorros in the Marianas Islands. A typical lesion could develop in as short a time as a month.

The margins of the diphtheritic ulcers were declivitous, indurated, and often rolled (figs. 37A and B, and 38). Occasionally, they were slightly undermined but not to the same extent as the tropical phagedenic ulcers described, for example, by James in the Melanesians.[24] Usually, there was a cone of induration, erythema, and bronze-violet pigmentation about the sharply defined sore (fig. 38).

In the India-Burma theater, a dry, black eschar was often noted similar to that of phenol burns or decubitus ulcers. In other instances, there was a fibrinous crust which when removed after the application of soaks revealed the lesion described. The eschar could usually be loosened at the edges but adhered firmly at the center as if it were a part of the subcutaneous tissue.

Usually, the base was relatively clean, with a moderate serous or serosanguineous discharge, but sometimes there was adherent fibrinopurulent material. The exudate beneath the crust was gray or gray green rather than yellow. Occasionally, there was a gray-green fibrinous membrane, which ordinarily was difficult to scrape from the surface but could be peeled off in some instances. It was present chiefly in lesions of short duration. This membrane was often fitted to the irregularities of the ulcer (fig. 39).

Under advantageous conditions, healing occurred by granulation from below and ingrowth of epithelium from the sides in such a manner that the scar was on a level with, or slightly below, the surrounding skin and only slightly less in diameter than the original lesion (fig. 37B, C, and D). At the center was a covering of thin white skin surrounded by a border of persistent bronze-violet pigmentation (fig. 37D). The latter tended to persist for months or years. Persistent hyposthenia or anesthesia in the scars was emphasized by some observers;[25] however, a degree of anesthesia in newly formed scar tissue is not surprising in any lesion.

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[24] James, C. S.: Tropical Phagaedenic Ulcer in the Pacific. Tr. Roy. Soc. Trop. Med. & Hyg. 31: 647-666, April 1938.

[25] See footnotes 12 (4), p. 281; and 19, p. 283.



FIGURE 37. Multiple diphtheritic ulcers of lower extremity acquired in New Zealand. The patient was given 300,000 units of penicillin in 5 doses per day intramuscularly for 18 days. Saline compresses (250 units per cc.) were applied for 4 hours twice daily. A. Appearance of lesions after 1 months' duration, before treatment, 21 May 1944. B. Lesions after 3 days' therapy. C. Appearance of lesions after 17 days' therapy. D. Lesions after 33 days of therapy.



FIGURE 38. Typical chronic ulcer of 4 weeks' duration. There was bronze-violet pigmentation of the surrounding skin. The patient acquired the lesion in the Solomon Islands.

These diphtheritic lesions were usually multiple (75 percent in the South Pacific series), and in almost all patients at least one lesion was situated on an extremity. In some instances, they were found in bizarre locations, as on the penis (fig. 40) or perianally. A large percentage of lesions were on the feet and as a result the ulcers were frequently disabling, although in other locations they caused little pain or inconvenience to the hardy soldier.

The largest lesion observed in the South Pacific group measured 40 by 15 mm. Occasionally, a very minute, but otherwise typical lesion was found to be diphtheritic. Recurrences were frequent, as the insensitive layer of newly formed skin was delicate and was subject to such trauma as may have been in part responsible for the ulcer originally. In recurrent lesions, a watery blister often formed at the center, but it usually did not contain *C. diphtheriae*.

In the majority of instances (55 percent in the South Pacific series, 85.1 percent in the India-Burma series) the onset of the ulcers was incident to combat or patrol activity and was uncommon in resting troops. Usually, there was a definite history of trauma, insect bite, or leech bite, but sometimes the lesion apparently originated in unbroken skin, in the same manner as impetiginous pustule.[26]

[26] See footnote 12 (4), p. 284.

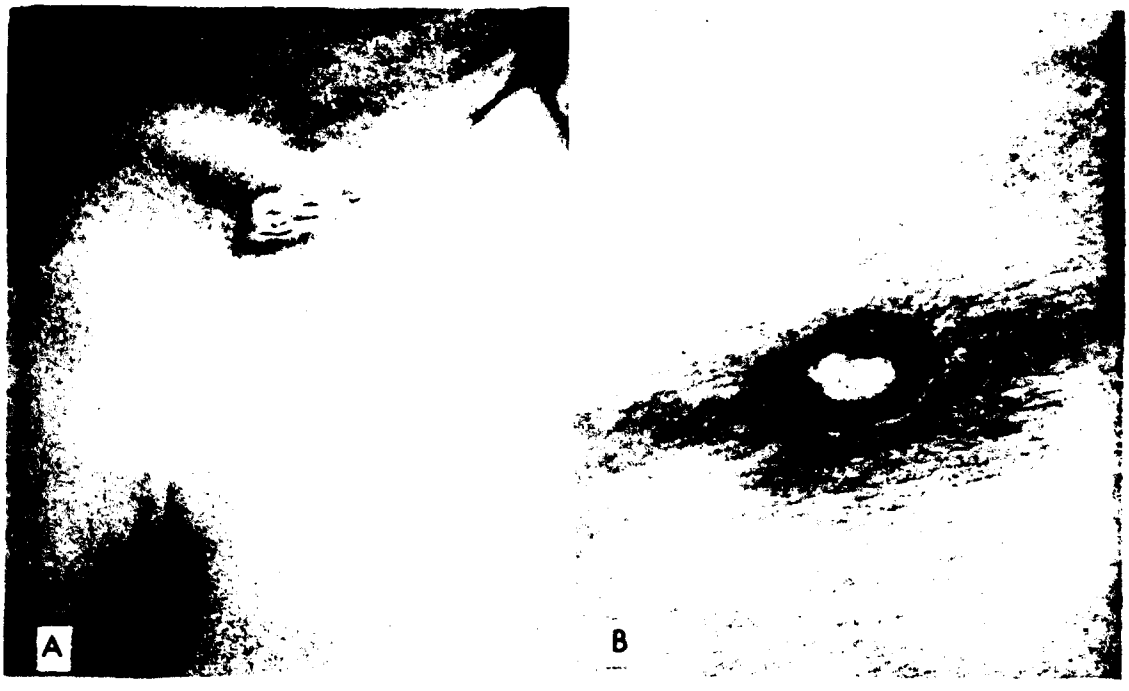


FIGURE 39. Diphtheritic skin ulcers. A. Skin ulcer over left clavicle with adherent green diphtheritic membrane. Patient acquired lesion in the Solomon Islands. B. Diphtheritic ulcer in skin over left iliac crest 13 weeks after onset. The lesion was relatively shallow but punched out with adherent gray-green membrane at the base. The lesion was acquired on the island of Saipan.

Atypical lesions. Although the diphtheritic lesions usually were of the punched-out, ulcerated character described, it was not uncommon in the tropics to culture *C. diphtheriae* from other varieties of skin lesions. Diphtheritic infection was observed in preexisting epidermophytosis of the feet (fig. 11). Occasionally, the opening of the tract was minute and the patient's discomfort disproportionately great. Five lesions of the interdigital spaces of the feet were noted in the India-Burma series. Any unexplained sinus tract of the feet in soldiers evacuated from the tropics should be suspected of being diphtheritic in origin.

Occasionally in the South Pacific and India-Burma groups and frequently in the Southwest Pacific,[27] *C. diphtheriae* was cultured from a diffuse, moist, ulcerative, and desquamative dermatitis (figs. 12 and 13).

Diphtheritic paronychias were occasionally observed, two each in the South Pacific and India-Burma areas. One was associated with a moist, diffuse, desquamative dermatitis of the extremities (fig. 13A); another (fig. 13B) was a contact lesion in a wardman at the 39th General Hospital, in the South Pacific, who daily dressed such a case for many weeks before the diphtheritic nature of the condition had been proved. There was rapid

[27] See footnote 12 (3), p. 281.

destruction of the nail, and in one of the Burma cases this seems to have been permanent.

MORPHOLOGY IN RELATION TO THE BACTERIOLOGY OF THE LESIONS

The observers in Burma [28] were of the opinion that the appearance of the punched-out ulcers was sufficiently characteristic to enable the diagnosis of cutaneous diphtheria to be made or ruled out, purely on clinical grounds, in a high percentage of cases. Evidence for this view was that, although toxigenic *C. diphtheriae* was cultured in only 21 percent of their cases, a

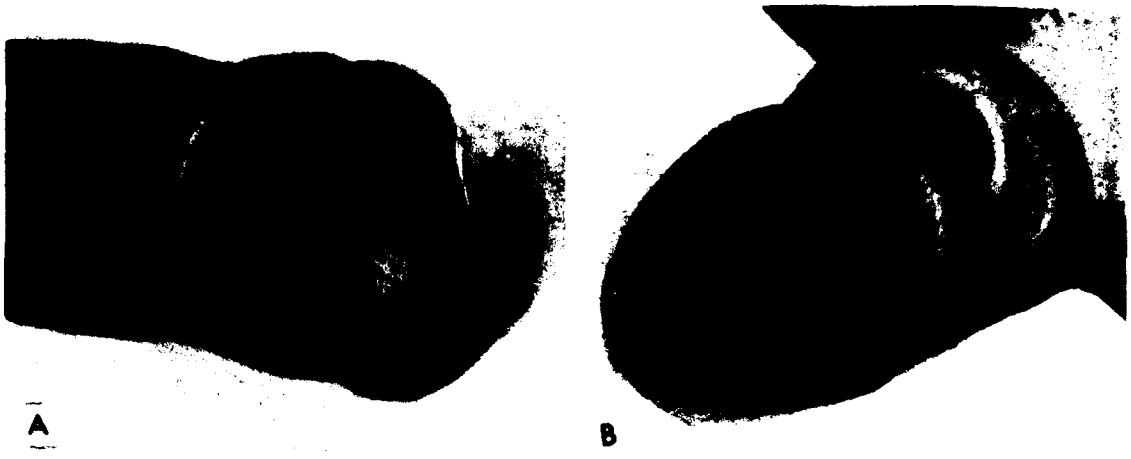


FIGURE 40.—Penile ulcers. A. Acute membranous diphtheria of coronal sulcus beginning 4 days *post fellationem*. B. Diphtheritic ulcer of penis resembling chancre in its firmness but has adherent green membrane from which toxigenic *Corynebacterium diphtheriae* was cultured. The patient had just returned from the Solomon Islands and had not indulged in sexual intercourse for more than 1 year.

very high percentage developed such complications as neuritis and carditis even when the cultures were negative. In the group of cases from Saipan, an attempt was made to predict from the clinical appearance of the lesions, before the results of culture became available, whether it would contain *C. diphtheriae*. A correct prediction was made in 69.1 percent of the attempts at judging 191 ulcerated lesions. This suggests that, in the age group concerned and in the territory under consideration, it was *C. diphtheriae* that played the important role in giving the lesions their characteristic morphological stamp, although no claim is made that the lesion is pathognomonic. The observers in the Southwest Pacific Area did not support this view and stated that there was no characteristic lesion.

Among the factors that may determine whether a culture positive for *C. diphtheriae* is obtained is the interval between the onset of the lesion and

[28] See footnote 12 (4), p. 281.

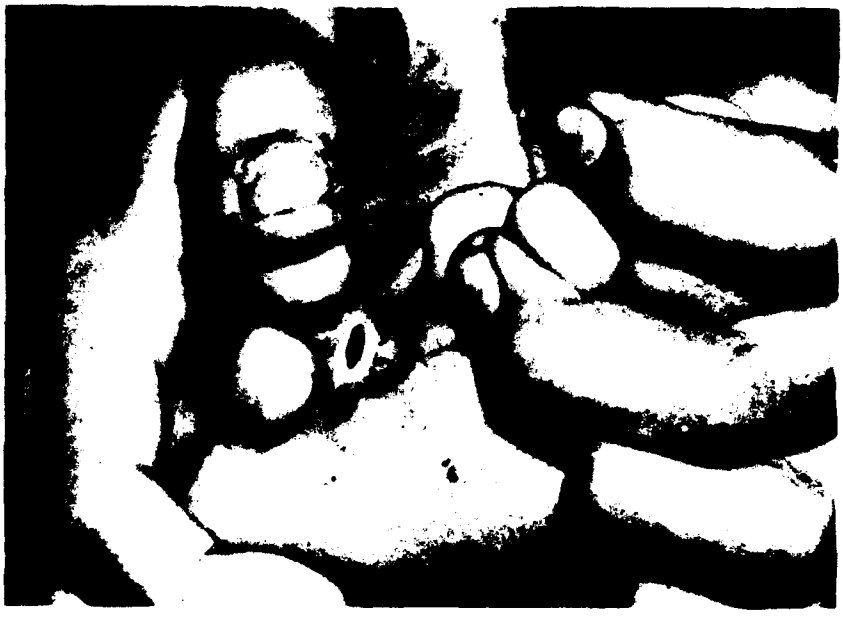


FIGURE 41.—Epidermophytosis superinfected with *Corynebacterium diphtheriae*. The indurated, rolled edge and deep cavity was characteristic of diphtheritic ulcers in this region. The lesion was acquired during the Battle of Saipan.

the time of culture. Thus, in the South Pacific series, there was an incidence of 26.3 and 23.4 percent of toxigenic micro-organisms in ulcerative lesions of two groups of soldiers, totaling 556 men, who were evacuated some 6 to 8 weeks after combat (when most of the ulcers were acquired), compared to an incidence of 6.2 percent in a group of 224 soldiers evacuated some 20 weeks after combat. In this study, all ulcerative dermatitides were cultured, although the lesion had the typical punched-out appearance. The observers in the India-Burma theater also stated that the chances of a positive culture decreased with the age of the lesion.

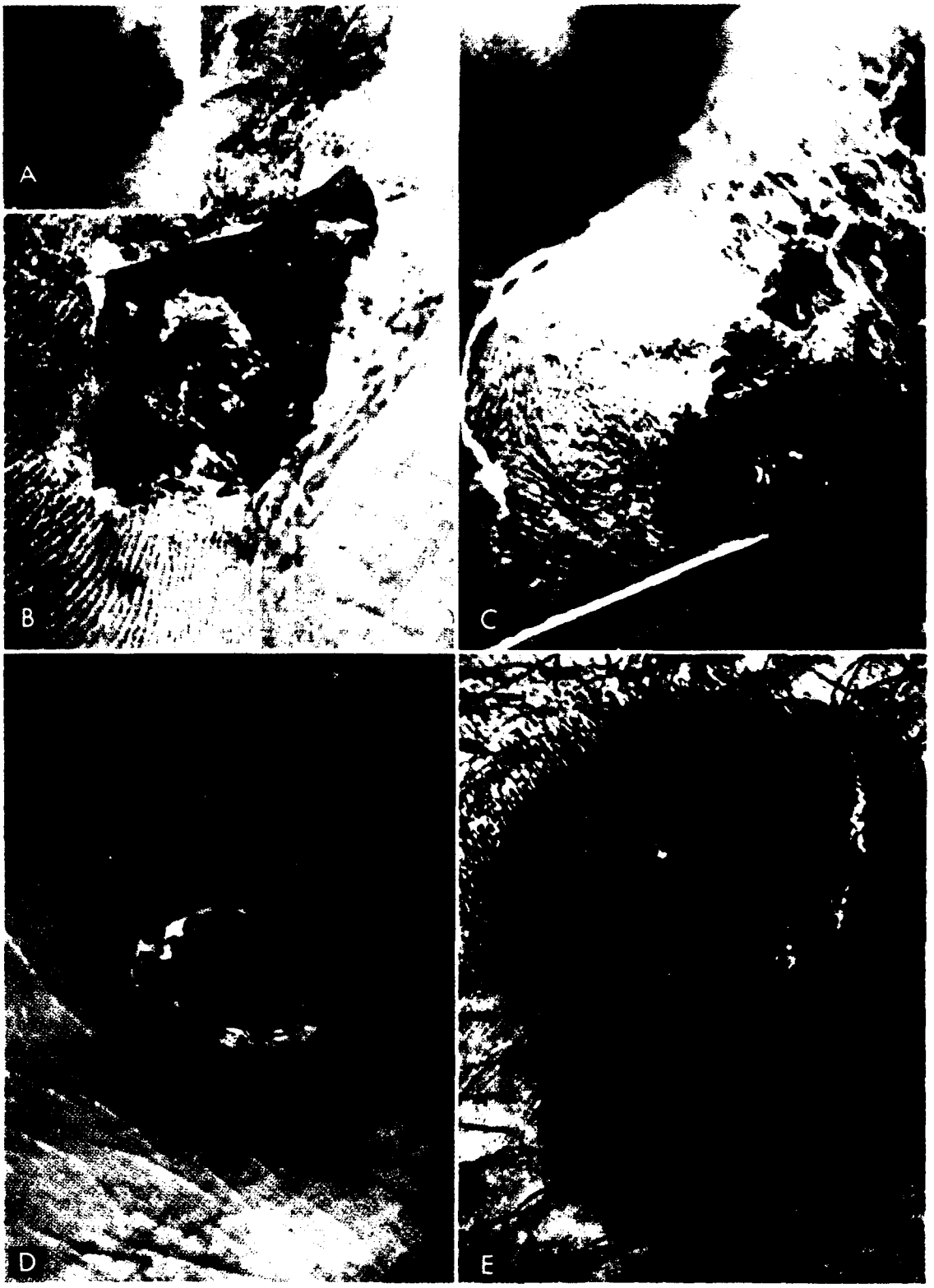
Another factor that may prevent finding *C. diphtheriae* in typical lesions is the application of various forms of treatment, especially penicillin, to which *C. diphtheriae* is sensitive. The analogy may be that the shovel that made the ditch is no longer there. In the Saipan group of the South Pacific series, 84.1 percent of lesions containing *C. diphtheriae* were grossly typical, but only 98 (53 percent) having ulcers thought clinically typical yielded *C. diphtheriae* on culture some 8 weeks after combat.

The duration of the lesions yielding a positive culture seems also to be a determinant of the toxigenicity of the strains recovered. Thus, in the South Pacific series, 40 of 43 (93 percent) diphtheritic ulcers of less than 12 weeks' duration yielded toxigenic micro-organisms, whereas of 25 older ulcers only 17 (68 percent) contained toxigenic bacilli. In one ulcer, a strain recovered on 18 November 1943 was toxigenic in contrast with one morphologically and biochemically identical obtained on 28 January 1944 from the



FIGURE 42.—Moist, desquamative, and ulcerative dermatitis. Virulent *Corynebacterium diphtheriae* from scalp and ulcers of leg. Lesion acquired in the Solomon Islands.

FIGURE 43.—Cutaneous diphtheria as seen in the India-Burma theater. The resemblance to the lesions shown in figures 37–42 in the South Pacific Area is striking. A. A recent lesion. The ulcer is still shallow and a thin layer of fibrinous material adheres to the base. The surrounding tissue is erythematous and moderately edematous. B. A black adherent eschar forms the center of the well-defined lesion. C. In another instance the eschar has been elevated revealing the punched-out character of the lesion and its relatively clean base. D. A more chronic diphtheritic ulcer retaining the punched-out character with relatively clean granulations at its base. The margin is indurated. The surrounding tissue is slightly edematous and has a bronze-violet color. E. A healed lesion. The slightly depressed thin scar has been covered by epithelium. A narrow zone of bronze pigmentation is seen.



See opposite page for legend.

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recurrent lesions. Similar observations were made in a case at the Moore General Hospital,[29] and the same general observation was recorded by the Southwest Pacific group, as follows: "In some instances, a culture early in the disease shows virulent organisms. Later, organisms with the same morphology and fermentation reactions were isolated, but were non-virulent by guinea-pig tests."[30] These observations indicate that the longer *C. diphtheriae* persist in a cutaneous lesion the less likely is the recovered strain to be toxigenic. This probably accounts for the relatively high incidence of atoxic strains in cutaneous lesions when seen in the United States.[31] Neuritis in individuals carrying avirulent *C. diphtheriae* suggests that they may at one time have harbored toxigenic micro-organisms. Carriers in general have a relatively high proportion of atoxic strains. The mechanism of this is not clear but may be based on the formation of atoxic variants.[32]

In the Saipan group, to determine whether both toxigenic and atoxic strains might coexist in the same lesion, two or three colonies from the primary plates were tested in each of five instances, but the various strains were all toxigenic. Toxigenicity was not lost in vitro when a series of micro-organisms, which had been stored on blood-agar slants in frigor for as long as 14 months with only one intervening transplantation, was retested.

There is a possibility that *C. diphtheriae*, which is not toxigenic for the rabbit or guinea pig, may have a destructive activity on the human skin. This is suggested by the work of Pasricha and Panja,[33] who injected micro-organisms, obtained from the "Garigha" sores of Assam, intracutaneously into other men. Ulcers resembling those of the donor patients resulted, while diphtheroids similarly inoculated produced no effect. These experiments require confirmation.

Other bacteria were usually associated with *C. diphtheriae* in the cutaneous lesions. Considering only the 145 ulcers from which toxigenic *C. diphtheriae* was obtained in the South Pacific group, 6 yielded pure cultures of *C. diphtheriae* on blood-agar plates, and in 84 others this was the predominant micro-organism. The associated bacteria in this group were almost invariably staphylococci (65 percent), beta hemolytic streptococci (47 percent), a new hemolytic corynebacterium (9.6 percent) belonging to the common group that includes the animal pathogens *Corynebacterium pyogenes* and *Corynebacterium ovis*, and other diphtheroids (4 percent). The new hemolytic corynebacterium was made the subject of a special study and is discussed on pages 293 and 319. The presence of beta hemolytic streptococci in such high incidence, both in the soldiers and in the natives, contrary to some opinions concerning the rarity of this micro-organism in trop-

[29] See footnote 17, p. 282.

[30] See footnote 12 (1), p. 281.

[31] See footnotes 17, p. 282; and 18 (1), p. 282.

[32] Dudley, S. F.: Critical Review. Schick's Test and Its Applications. Quart. J. Med. 22: 321–379, January 1929.

[33] Pasricha, C. L., and Panja, G.: Diphtheritic Ulcers of the Skin: The "Garigha" of Chittagong Hill Tracts. Indian J.M. Research 27: 643 650, January 1940.

ical environments, is of interest. At Harmon General Hospital[34] almost all of the 56 ulcerated dermatitides under study had cultures positive for hemolytic *Staphylococcus aureus*, but less than 10 percent were positive for beta hemolytic streptococci.

METHODS OF DIAGNOSIS

Early difficulties.—Until educative efforts emanating from higher medical echelons became effective, or until suspicion was raised by the development of suggestive complications or nasopharyngeal infection in contacts, there was great delay in accepting any of the cutaneous lesions of the tropics as diphtheritic. In the words of Col. William S. Middleton, MC,[35] Chief Consultant in Medicine, Office of the Chief Surgeon, European theater, "a new generation in medicine has grown up without clinical awareness of the disease [diphtheria]." Part of the difficulty resulted from burying reason in the shroud of obscurant nomenclature, such as tropical ulcer, ecthyma, or "Garigha," and veldt or "Naga" sores. These exotic local names for a condition general in the tropics fostered the expectation of an exotic etiology. Part of the difficulty, however, resulted from inadequate bacteriological diagnosis, for few laboratory officers had had extensive experience with *C. diphtheriae* in the United States. In one general hospital, where an alert clinical staff had correlated expert dermatological knowledge with the observation of a large number of cardiac and neurological complications suggestive of diphtheria, there were no positive reports of skin cultures for *C. diphtheriae* during the first 6 weeks of observation of a large number of patients. Subsequently, positive bacteriological diagnosis of *C. diphtheriae* was made in approximately 60 percent of the cases.[36]

Technique of cultures.—In experienced hands, the simplest methods of culture were effective. It was found best to bring the media to the bedside and to remove a small quantity of material from the base of the ulcer with a platinum loop filled with saline or broth, if necessary. It was not important to get beneath overhanging margins or to scrape deeply. The bacteria were everywhere over the surface of the granulations at the base. If the ulcer was relatively clean and not crushed, direct culture of the base was successful without further preparation, and it was not necessary to apply alcohol or other agents. It was far more satisfactory as a routine procedure in hospital cases to apply a warm saline pack to the lesion from 3 to 24 hours, which helped to remove any excessive exudate, fibrinous crust, or ointment that may previously have been applied. Saprophytic bacteria were relatively abundant in the protein material of the external parts of the exudate.

Corynebacterium diphtheriae in smears.—In smears from the lesions,

[34] See footnote 18 (1), p. 282.

[35] Semiannual Report, Chief Consultant in Medicine, Office of the Chief Surgeon, Headquarters, European Theater of Operations, U.S. Army, 1 Jan.–30 June 1945.

[36] See footnote 12 (1), p. 281.

C. diphtheriae was often found within polymorphonuclear leukocytes of the exudate (fig. 43C). Sometimes, the micro-organisms were numerous, and the predominant element of the bacterial population, but usually there was an admixture of gram-positive cocci in chains and clumps. In exudates, the micro-organisms were observed frequently to be stouter than in the classical descriptions, which are based on the appearance of the bacteria on Löffler's medium (fig. 43D). The bacteria from cutaneous lesions assumed the classical forms when grown on this material. In the tropics, great difficulty was encountered in distinguishing *C. diphtheriae* from the new hemolytic corynebacterium that was so frequently found in these lesions as well as in infections of the throat. *C. diphtheriae* could usually be differentiated from ordinary diphtheroids, since the former were longer, more pleomorphic, with slender and club-shaped forms, more granular, and less intensely gram positive.

With the Saipan group, an attempt was made to determine how well purely morphological criteria would bear the test of subsequent bacteriological investigation. In smears of exudate from 150 ulcers, the presence or absence of *C. diphtheriae* was correctly predicted in 83.3 percent. In 10 instances, 6.7 percent, the characteristic bacilli were not seen in direct smears but were found in the cultures. In 15 instances, 10 percent, gram-positive pleomorphic bacilli were incorrectly diagnosed as *C. diphtheriae* from the smears. This demonstrates that, with experience, a reasonably accurate guess can be made, which may apply under field conditions where facilities for culture are not available.

Bacteriological media.—With the proper use of blood-agar plates, isolated colonies could be studied and picked for subculture, usually within 24 hours. It was found important—

1. To adjust the pH of the agar to 7.6 before sterilizing, since *C. diphtheriae* grows better on slightly alkaline media.

2. To cool the medium to 45° C. or less before adding fresh blood. If the blood is overheated, the narrow ring of hemolysis characteristic of *C. diphtheriae* type *mitis* may be obscured and the colonies are less readily distinguished from those of staphylococci and diphtheroids.

3. To employ good streaking technique, so that the colonies on the plate were well isolated and did not present the cream cheese confluence too often characteristic of routine plates in badly conducted laboratories. On this medium, the differentiation from the unusual corynebacterium is simple, for the latter produces intensely hemolytic colonies resembling those of the beta hemolytic *Streptococcus*.

Löffler's serum was found useful when examined 8 to 12 hours after incubation, for then *C. diphtheriae* appears in long slender pleomorphic form, permitting a tentative differentiation from the generally much shorter and thicker diphtheroids. It was extremely difficult, however, to distinguish *C. diphtheriae* from the new hemolytic corynebacterium.

Tellurite medium, particularly Müller's modification,[37] was very successful in some hands. The difficulty with this medium was that some batches of crystalline potassium tellurite supplied early in World War II seemed to have become partly decomposed during the vicissitudes of transportation through the Tropics and were more toxic for *C. diphtheriae*. On this medium, there was often a delay of up to 48 hours before typical colonies of *C. diphtheriae* made their appearance. The advantages under ideal circumstances are the selectivity of tellurite aiding differentiation of the type of *C. diphtheriae*. The new hemolytic corynebacterium generally was markedly inhibited on this material.

In the India-Burma theater, contrary to experience elsewhere where *mitis* was found, the micro-organisms were described as being of the *intermedius* variety.[38] In the same theater, at the 20th General Hospital, 90 percent of micro-organisms described as virulent *C. diphtheriae* were said to ferment sucrose but not dextrose or levulose. In the South and Southwest Pacific[39] experiences, all of the virulent *C. diphtheriae* were sucrose nonfermenters.

ASSOCIATED CLINICAL FINDINGS

It was noted by all observers that, aside from the complications of neuritis and myocarditis, there were usually no general symptoms of intoxication when the ulcers alone were the seat of *C. diphtheriae*. The patients usually complained of nothing more than local discomfort, if that.

In rare instances in the South Pacific group, there was an unexplained tachycardia. One had a persistent elevation of the pulse rate to as high as 120 per minute on complete bed rest, without fever or changes in the electrocardiogram. The tachycardia disappeared as the ulcers healed.

It was noted by the observers in Burma that the general feeling of well-being may have contributed to the psychoneurotic state observed in some patients whose hospitalization was prolonged because the ulcers failed to heal or because there was a recurrence during attempts at reconditioning.[40]

Suppurative adenitis or lymphangitis were remarkably rare despite the presence not only of virulent *C. diphtheriae* but frequently of hemolytic *Staph. aureus* or beta hemolytic streptococci. Moderate local swelling of the lymph nodes without heat, however, was frequent.

In two Schick-positive individuals, a striking erythema and edema occurred about the ulcers following administration of diphtheria antitoxin. This may be analogous to the Francis reaction as observed in pneumococcal infections.

Hyperhidrosis of the hands and feet in association with cutaneous diphtheria was noted by the Burma group in 13 percent of the patients.

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[37] Medical Bulletin No. 2, Office of the Theater Chief Surgeon, Headquarters, Theater Service Forces, European Theater, January 1946, pp. 21–24.

[38] See footnote 12 (1), p. 281.

[39] See footnote 16, p. 282.

[40] See footnotes 12 (4), p. 281; and 13, p. 281.

RELATION TO THE SCHICK REACTION

The relation of the incidence of the lesions to the Schick reaction of the individual is of considerable interest, as it has both etiological and prophylactic connotations. It was found in the South Pacific experience that individuals with diphtheritic ulcers are much more frequently Schick positive than the general population of which the patients are a part (table 43). This indicates that the Schick-negative stage is in large measure protective. At the Moore General Hospital, 13 of the 18 patients with virulent *C. diphtheriae* in their cutaneous lesions had positive Schick reactions. These lesions had been present for as long as 4 months. All of those at the Harmon General Hospital, however, had negative Schick reactions. In another large group in the India-Burma theater (69th General Hospital), 40 percent of infected individuals were Schick positive, while 20 percent of uninfected individuals in a random sampling of admissions were Schick positive. It is notable that the divisions, after combat service in the Tropics, have a lower incidence of Schick-positive individuals than the 35 to 45 percent before going overseas. On the dermatology ward at a large hospital in the United States, 34 percent of patients from the Pacific admitted with this disease were Schick positive in contrast with the 75 general medical admissions from the Pacific areas, of whom only 13.3 percent were Schick positive. Thirty-two percent of the individuals harboring avirulent *C. diphtheriae* were Schick positive. This suggests a general, largely subclinical, diphtherization anologous to that which Dudley found in his school studies. Bensted,[41] during an outbreak of diphtheria among British troops in northwest India, performed Schick tests on his battalion and observed that all of those subsequently developing diphtheritic ulcers were Schick positive.

TABLE 43.—*Schick reactions of individuals with diphtheritic tropical ulcers in three infantry divisions in the South Pacific Area*

Infantry division	Ulcers containing toxigenic *C. diphtheriae*		Ulcers containing atoxic *C. diphtheriae*		Reactions	
	Number tested	Percent positive	Number tested	Percent positive	Number tested	Percent positive
25th and 43d combined	57	42.1	14	28.5		
25th					9,000	21.0
43d					11,968	27.8
27th	74	20.3	12	8.5	12,135	11.0

Source: Liebow, A. A., MacLean, P. D., Bumstead, J. H., and Welt, L. G.: Tropical Ulcers and Cutaneous diphtheria. Arch. Int. Med. 78: 255-295, September 1946.

[41] Bensted, H. J.: A Limited Outbreak of Diphtheria Exhibiting Both Cutaneous and Faucial Lesions. J. Roy. Army M. Corps 67: 295-307, November 1936.

Several instances, however, have been recorded of the development of diphtheritic ulcers in Schick-negative individuals. One patient in the 27th Division had been found Schick negative 1 month before admission for a diphtheritic ulcer of 2 weeks' duration. In the India-Burma theater, one patient, a medical officer, who was known to have had a negative Schick test before he acquired the infection, later developed postdiphtheritic neuritis and myocarditis. In the same group, there was another man, previously Schick negative, from whose ulcers toxigenic *C. diphtheriae* was cultivated. Two Schick-negative individuals in whom cutaneous diphtheria appeared are mentioned in the April 1945 report from the 69th General Hospital in the India-Burma theater. One had been Schick negative 4½ months before the cutaneous lesion developed at the site where he had been scratched by a psychotic Chinese soldier patient. The other was a cook who had been found Schick negative 3 weeks previously; he had suffered a laceration from tripping over a crate. These cases, as well as others in which the Schick reaction was negative within 1 to 5 days after apparent onset, indicate that a negative Schick reaction does not necessarily imply immunity to cutaneous diphtheria and its complications.

The interpretation of a Schick-negative reaction in an individual with established ulcers is difficult. The Schick-negative state may either have existed at the time the skin became infected or it may have been induced by the micro-organisms resident in the skin.

Certain patients have positive Schick reactions despite the fact that ulcers containing toxigenic *C. diphtheriae* have existed for many months. This suggests that the skin is not a good absorbing surface for the toxin. It has long been known that a single attack of pharyngeal diphtheria fails to reverse the Schick reaction in about 60 percent of persons retested 3 to 4 months after recovery. Further evidence that the skin does not absorb toxin as efficiently as the pharynx is the long latent period before neuritis develops in the purely cutaneous cases (p. 301).

CUTANEOUS AND EXTRACUTANEOUS DIPHTHERIA

Incidence.—The concomitance of cutaneous and extracutaneous diphtheria has been noted previously, especially by Bensted, and Cameron and Muir[42] in the Middle East. In the South Pacific studies, routine cultures of the nose and throat of 174 patients with diphtheritic ulcers revealed *C. diphtheriae* in 19 (11 percent) of them. This is a much higher carrier rate than in the general military population of which these patients were a part. Ten of the nineteen individuals had clinical pharyngeal diphtheria, and two had fibrinous rhinitis. There were also six pharyngeal carriers and one nasal carrier. In the India-Burma series, only 1 of the 119 patients with ulcers had virulent *C. diphtheriae* in the throat, but 8 others had diphtheroids re-

[42] Cameron, J. D. S., and Muir, E. G.: Cutaneous Diphtheria in Northern Palestine. Lancet 2: 720-723, 19 Dec. 1942.

sembling *C. diphtheriae*. There was another patient with both faucial and cutaneous lesions who was not included in the series.

Autoinfection of nasopharynx from the skin.—In the India-Burma series, two questionable faucial involvements occurred more than 6 weeks after the onset of postdiphtheritic neuritis, which apparently resulted from cutaneous diphtheria.

In 3 of the 12 clinical cases of the South Pacific group mentioned previously, the patients had been sent to the hospital for the treatment of ulcers and were found to be Schick positive. Acute pharyngitis developed while the patients were in strict isolation for periods varying from 2½ to 5 weeks. All three had had negative throat cultures and were not given antitoxin until the pharyngitis became manifest. These cases demonstrate that in all probability autoinfection of the nasopharynx from the skin can occur. The other clinical cases were admitted primarily for pharyngitis or rhinitis, although in five of them ulcers antedated the diphtheria of the throat for periods varying from 3 to 7 weeks.

In 27 pharyngeal cases observed at the 122d Station Hospital in the New Hebrides, 14 (52 percent) had had skin ulcers that antedated the nasopharyngitis from 1 week to 3 months. In the newly described British series of 76 cases of cutaneous diphtheria, 12 were coincident infections of the skin and throat. In nine of these, the skin infection definitely preceded that of the throat or nose.

COMPLICATIONS

Incidence.—The incidence may be described as actual and apparent.

1. The actual incidence of complications, as well as the severity of the disease, is determined by the toxigenicity of the micro-organisms and by the level of susceptibility of the population. Dudley in particular has pointed out how susceptibility, by a process of latent immunization, tends to fall in an environment where *C. diphtheriae* is widely disseminated. Evidence that this has occurred in the Tropics is the Schick reaction of veterans of the Pacific campaigns as compared with those of trainees.

2. The apparent incidence, given constant factors of toxigenicity and susceptibility, is determined by the accuracy with which all cases of diphtheria, complicated and uncomplicated, are diagnosed. This has been especially true in the Tropics, where the clinical manifestations frequently have been very mild (as described by Norris and his coauthors) and where, as a consequence, skillful bacteriological technique is particular necessary. Many cases of diphtheria have been dismissed as ordinary nasopharyngitis when routine cultures are not taken. Brigadier Dorland of the British Army has expressed this point in remarking about the apparent high incidence of complications. In 48 cases of faucial diphtheria at the 9th General Hospital on Biak, Oppel found only 5 with typical membrane. In this hospital, in February 1945, *C. diphtheriae* were found in the throat of 12 of 24 cases of acute

pharyngitis or tonsillitis; common colds were not included in this series. So mild had the diphtheria been that it was actually the presence of typical complications that first drew attention to the existence of the infection, which previously had escaped bacteriological detection. This mildness is probably the result of latent immunization. Obviously, the apparent incidence of complications will be high if, because of inferior bacteriological technique, few diagnoses of diphtheria are made.

In any particular series, it is difficult to state whether this factor or toxigenicity and susceptibility have determined the stated incidence of complications, but all of these possibilities should be kept in mind.

Diphtheritic neuritis.—Diphtheritic neuritis was reported from many parts of the world, especially from tropical regions, during World War II. Such factors as have been mentioned in the preceding section probably account for the following variations in the stated incidence of the postcutaneous form: South Pacific Area, 3 of 85 patients (4 percent); Southwest Pacific Area, 6 of 102 patients (6 percent); India-Burma theater, 61 of 141 patients (43 percent) at the 20th General Hospital and 19 of 40 patients (48 percent) at the 69th General Hospital.

Since the differential diagnosis and detailed clinical description are presented in another volume in the history of the Medical Department in World War II,[43] no more than a few general remarks will be made here. Caution must be exercised in accepting neuritis as a complication of cutaneous diphtheria. The minimal evidence that neuritis is of cutaneous rather than nasopharyngeal origin is the demonstration of *C. diphtheriae* in the skin and its absence in the nose and throat. Gathering this evidence has been neglected in many series of cases, including the earliest ones of Walshe.[44]

Cultures of all known foci of diphtheritic infections are especially important in view of the mildness of the nose or throat symptoms in some cases, especially of anterior nasal diphtheria, where crusting and nasal discharge may be minimal. It must be remembered, however, that even if the microorganisms are found only in the skin they may at one time have been present in the nasopharynx where they may no longer be demonstrable. This is emphasized by the fact that in some series it has been specifically stated that the patients spontaneously mentioned neither the sore throats nor the skin lesions in giving an account of the symptoms antecedent to the first neurological illness.[45] Thus, in some series of cases it is not possible to state to which variety of diphtheria the neurological complications are related.

In contrast to the nature of the complication following pharyngeal diphtheria, the cranial nerves, particularly the ninth, were rarely involved in cases proved to be purely cutaneous. It was generally true also in Samp-

[43] Medical Department, United States Army. Internal Medicine in World War II. Volume III. Infectious Diseases and General Medicine. [In preparation.]

[44] Walshe, F. M. R.: Post-Diphtheritic Paralysis. Note on a Form Following Cutaneous Diphtheria. Lancet 2: 232-233, 24 Aug. 1918.

[45] Perkins, R. F., and Laufer, M. W.: Clinical Study of Postdiphtheritic Polyneuritis. J. Nerv. & Ment. Dis. 104: 59-65, July 1946.

son's series of 20 cases, and a similar impression was held by Quillinan,[46] although no detailed evidence was presented. This may be less true of paralysis of accommodation, which is transient, and in which especially skillful observation is necessary, than of pharyngeal paralysis. There is no doubt that diphtheritic neuritis can occur in individuals with positive Schick reactions. Apparently, in some instances, the toxin is absorbed upon the nervous tissues sufficiently to result in neuritis, while not enough antitoxin is stimulated to reverse the Schick reaction. Generally speaking, a single clinical attack of nasopharyngeal diphtheria fails to reverse the Schick reaction in approximately 60 percent of cases. Low antibody levels do not preclude previous, even relatively recent, diphtheritic infections, as Bronson[47] would imply. This is pointed out by the observations of Gammon and Schoenbach. In Bronson's series, it is mentioned that 80 percent of proved cutaneous diphtheria, even of long duration, had positive Schick reactions. Also, Bronson mentioned a patient with nasopharyngeal diphtheria who was Schick positive 3 months after the infection and who had had antitoxin for treatment in the meantime. Three in Sampson's series had positive Schick reactions at the time the neuritis was diagnosed, but in these cases *C. diphtheriae* was not demonstrated. In the 20th General Hospital group, all patients with definite complications had negative Schick tests.

In most cases of undoubted diphtheritic neuritis, there is an elevation of spinal fluid protein, sometimes with changes in the colloidal gold curve, but almost always without pleocytosis.[48] In Delp, Sutherland, and Hashinger's[49] cases, the spinal fluid protein levels varied between 57 and 230 mg. percent. The average in Perkins and Laufer's[50] series of 21 cases was 114 mg. percent, but some were as high as 200 mg. percent. In Sampson's group of 20 instances, most of which were postcutaneous, approximately one-third were below 40 mg. percent, the others were higher, and the maximum was 134 mg. percent. In the India-Burma series, the proteins were described as elevated in nearly every case and in general "proportional to the severity of the neurological disease."[51] This so-called albuminocytological dissociation has caused a great deal of confusion, and much neuritis of diphtheritic origin has been classified under the Guillain-Barré syndrome, rather than under the etiological diagnosis. Often, this has been in flagrant disregard of the principle that eponyms should be applied only to the syndrome as originally described. A part of the confusion has arisen from lack of knowledge of

[46] Medical Bulletin No. 2, Office of the Theater Chief Surgeon, Headquarters, Theater Service Forces, European Theater, January 1946, pp. 19–20.

[47] Bronson, L. H.: On the Etiology of Neurological Disease Following Infections of the Throat and Skin and the Incidence of Diphtheritic Infections. Arch. Neurol. & Psychiat. 56: 558–566, November 1946.

[48] (1) See footnote 8, p. 279. (2) Rankin, J. H.: Diphtheritic Polyneuropathy. ETO M. Bull. 32: 32–35, July-August 1945.

[49] Delp, M. H., Sutherland, G. F., and Hashinger, E. H.: Post-Diphtheritic Polyneuritis: A Report of Five Cases With Albuminocytologic *Dissociation Simulating* Guillain-Barré's Syndrome. Ann. Int. Med. 24: 618–628, April 1946.

[50] See footnote 45, p. 299.

[51] See footnote 12 (4) and (6), p. 281.

cutaneous diphtheria and its scars. Also, there has been ignorance of the fact that a positive Schick reaction is not incompatible with diphtheritic neuritis. The greatest cause of the difficulty, however, has been inadequate bacteriological diagnosis of cutaneous and mild nasopharyngeal diphtheria. These remarks must not be construed to imply that there were no other causes of neuritis among U.S. soldiers; some had all of the features of the syndrome as originally described by Guillain, Barré, and Strohl.[52] It is desired to emphasize here, however, that the vast majority of cases of neuritis seen in the tropics were diphtheritic in origin.

In the South Pacific series, it was considered desirable to subdivide the cases of neuritis, as follows:

Group A.—Neuritis complicating proved cutaneous diphtheria without evidence of *C. diphtheriae* elsewhere.

Group B.—Neuritis associated with ulcers of the skin unhealed at the time of admission but not demonstrated to contain *C. diphtheriae.*

Group C.—Neuritis in individuals with scars of tropical ulcers.

Group D.—Neuritis in individuals with scars of tropical ulcers and history of sore throat.

Group E.—Neuritis in individuals proved to have diphtheritic pharyngitis.

Group F.—Other cases of neuritis clinically indistinguishable from diphtheritic neuritis.

After the diphtheritic nature of certain tropical ulcers became apparent, there was no instance of neuritis of the type discussed that could not be related either to the ulcers, sore throat, or to proved diphtheritic pharyngitis or dermatitis.

Notable in cutaneous diphtheria is the long incubation period of neuritis. In the three cases in group A of the South Pacific series, the symptoms began between 3 and 7 months after the lesion was first noted by the patient. In two of the patients, the lesion occurred 2 and 4 months, respectively, from the time that the toxigenic *C. diphtheriae* was first cultured from the lesion. In pharyngeal diphtheria, neuritis most commonly begins within 6 weeks after onset of sore throat. In a series of 21 cases of neuritis observed at a neurological center in the United States, the average time of appearance of the neurological symptoms after onset of the nasopharyngeal disease was 26 days, whereas it was 2½ months after the onset of the cutaneous lesion.[53] There is some variation in this, since in another group at the Baxter General Hospital[54] the incubation period of the cutaneous cases varied between 30 and 77 days, and of the pharyngeal cases between 30 and 72 days. The interval between the onset of the ulcers and the onset of the

[52] Guillain, G., Barré, J. A., and Strohl, A.: Sur un syndrome de radiculo-névrite avec hyperalbuminose du liquide cephalo-rachidien sans réaction cellulaire. Remarques sur les caractères cliniques et graphiques des réflexes tendineux. Bull. et mém. Soc. méd. d. hôp. de Paris 40: 1462–1470, 13 Oct. 1916.

[53] See footnote 45, p. 299.

[54] See footnote 19, p. 283.

neuritis in the India-Burma series was 68 days in the 20th General Hospital group and 73 days in the referred patients. It was of the same order of magnitude at the 69th General Hospital in the same theater.[55] In a reported British experience in North Africa,[56] an interval of 6 to 10 weeks elapsed in most cases after the skin lesions were noted and before the neurological symptoms appeared.

The duration of the neurological symptoms is considerable. In Sampson's series, it varied between 50 and 155 days. In the India-Burma group, the average case lasted 100 days.

Among the interesting clinical manifestations is the fact that, contrary to other varieties of neuritis, persistent muscle weakness was rare. One instance, however, is reported by Sampson in which there was residual paralysis of the serratus anterior and deltoid muscles. The group at Baxter General Hospital observed a partial electrical reaction of degeneration in all of the severe cases. Pain was a most unusual symptom.

Carditis in cutaneous diphtheria.—Myocarditis has come to be the most important cause of death in diphtheria. During World War II, tissues from 221 cases of diphtheria were sent to the Army Institute of Pathology (now the Armed Forces Institute of Pathology), Washington, D.C., for study.[57] There was evidence of myocarditis in 143 or 65 percent of these cases. By 1945, postdiphtheritic myocarditis had become an important cause of death among troops in the army of occupation in Germany. At the 7th Medical Laboratory,[58] Gräfelfing, Germany, it was the cause of death in 12 of the 285 post mortem examinations reviewed, and at the 4th Medical Laboratory,[59] Paris, France, in 15 of 1,021 autopsies. In all but 1 of these 27 fatal cases of myocarditis, antitoxin had been administered 5 or more days after the onset of diphtheria, if at all. Cutaneous diphtheria also was complicated by myocarditis, as seen in eight of the deaths in the Army Institute of Pathology series with such a pathogenesis.

In the India-Burma group of 141[60] cases of cutaneous diphtheria, indubitable evidence of carditis existed in four instances, one of which came to autopsy, and of probable myocarditis in three, a total incidence of 5 percent. In seven others, there were suggestive findings in the electrocardiographic tracings, but the diagnosis could not be definitely established. All individuals with definite myocarditis had extensive skin lesions. A program of case finding was instituted which included a careful physical examina-

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55 See footnote 14 (1), p. 281.

56 See footnote 7 (2), p. 279.

57 Gore, I.: Myocardial Changes in Fatal Diphtheria; Summary of Observations in 221 Cases. Am. J.M. Sc. 215: 257-266, March 1948.

58 Medical Bulletin No. 2, Office of the Theater Chief Surgeon, Headquarters, Theater Service Forces, European Theater, January 1946, pp. 14-18.

59 Medical Bulletin No. 1, Office of the Theater Chief Surgeon, Headquarters, Theater Service Forces, European Theater, December 1945, pp. 19-23.

60 (1) Kay, C. F.: Myocardial Complications of Cutaneous Diphtheria. [Official record.] (2) Kay, C. F., and Livingood, C. S.: Myocardial Complications of Cutaneous Diphtheria. Bull. U.S. Army M. Dept. 4: 462-464, October 1945.

tion, as well as electrocardiographic tracings, as soon as possible after the diagnosis of cutaneous diphtheria was made, and at intervals of 15 to 30 days thereafter until well after the lesions had become inactive. In the same group of 141 individuals, the incidence of neurological complications was 43.5 percent. All four of those with definite myocarditis had neuritis. Neuritis usually preceded myocarditis except in the one fatal case. The earliest appearance of the electrocardiographic changes was on the 20th day of the existence of the cutaneous lesion; in the fatal case, the severe symptoms appeared on the 38th day, followed by death 3 days later; and in another case, myocarditis appeared on the 60th day. The duration of electrocardiographic changes was from 60 to 90 days among those in whom the diagnosis was certain and approximately 30 days in those in whom the diagnosis was considered probable. The incubation period was shorter in the postpharyngeal cases.[61]

The clinical findings were usually minor. Four patients in the India-Burma group were asymptomatic, two complained of dyspnea and faintness on slight exertion, and the one who died first suffered abdominal pain with nausea and dyspnea on exertion. Eighteen hours before death, discomfort extended upward into the chest, then there was vomiting, collapse, fall in blood pressure, gallop rhythm, and leukocytosis. The electrocardiographic tracings usually did not show a P–R interval in excess of 0.20 second, nor were abnormalities in the QRS segment striking. The most consistent abnormalities were depression or frank inversion of T-waves in the C–R3 lead. These occurred in all but the fatal case of the India-Burma group. This was also the experience of Ball who emphasized depression of the S–T interval. Conduction defects apparent in the two cases of myocarditis that followed nasopharyngeal diphtheria were not observed among the post-cutaneous cases in the India-Burma group, but they were described in other instances that apparently followed diphtheria of the skin.[62]

Several writers have stressed the importance of serial electrocardiographic tracings to diagnosis.[63] Careful observations of pulse and blood pressure must, however, not be forgotten.

Delp and Dimond, who were successful in treating two severe cases of myocarditis, emphasized the importance of putting the patients at absolute rest, elevating the foot of the bed, applying external heat, and slowly administering glucose solution by vein.

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61 (1) Ball, D.: Diphtheritic Myocarditis; With Report of 2 cases. Am. Heart J. 29: 704–707, June 1945. (2) Craig, C. McK., and Manch, M. D.: A Study of the Aetiology of the "Desert," Septic, or Veldt Sore Amongst European Troops; And Its Association With Faucial Diphtheria. Lancet 2: 478–479, 13 Sept. 1919. (3) Delp, M. H., and Dimond, E. G.: Diphtheria and the Heart. J. Kansas M. Soc. 47: 254–259, June 1946. (4) See footnote 60 (1), p. 302.

62 (1) Greene, R. C.: Combined Sulfonamide and Diphtheritic Myocarditis in Cutaneous Diphtheria. Am. Heart J. 32: 250–256, August 1946. (2) Solomon, S., and Irwin, C. W.: Cutaneous Diphtheria With Toxic Myocarditis; Report of Fatal Case With Necropsy Findings. Ann. Int. Med. 26: 116–120, January 1947.

63 See footnotes 61 (3), above; and 60 (1), p. 302.

TREATMENT OF CUTANEOUS DIPHTHERIA

Case finding and methods of study.—After the high incidence of cutaneous diphtheria in tropically acquired cutaneous infections was recognized, and particularly after the dangers of contact cases were realized, relatively efficient methods of case finding were instituted. These consisted in temporarily isolating all patients with ulcerative dermatitis and making cultures designed to detect *C. diphtheriae*. In some institutions, new patients were held on a special admission ward. Routine cultures were made from material from the cutaneous lesions and from the nose and throat. If the culture was positive for *C. diphtheriae*, the patient was treated specifically in isolation until virulent organisms were no longer recovered. The other patients were released for treatment in a general dermatological ward. Such a method was found valuable in the South Pacific study in handling the heavily infected 27th Division in the New Hebrides rest area. After a series of talks designed to acquaint the battalion surgeons with diphtheria of the skin, a centrally located clinic was established to which all patients with tropical ulcers were referred for culture. Those found positive were hospitalized. In this way, many patients were put under treatment, and the dissemination of the organisms was checked. This procedure was especially effective in curbing contact cases. Oppel and his coworkers reported that a similar method was adopted in the Southwest Pacific Area. Individuals who were found to have cutaneous lesions infected with *C. diphtheriae* and were Schick positive were treated with antitoxin. The procedure at Moore General Hospital and at Harmon General Hospital was similar. The desirability of making nose and throat cultures in such cases was stressed in these institutions, as was also the use of Schick-negative attendants in caring for them.

Antitoxin.—During the Second World War, serum therapy was not productive of remarkable results in the local lesions so far as could be determined by observers of wide experience. Certainly, serum was not lethal to the organisms, which may persist for many days after treatment. At Moore General Hospital, it was necessary to keep patients isolated for an average of 61 days, whether or not antitoxin had been administered. Antitoxin, however, may act as a prophylactic in preventing the serious consequences of autoinfection of the nose and throat. Also, experience in the India-Burma theater indicated that antitoxin, even when given late in the course of a cutaneous infection, seemed to be valuable in preventing complications (table 44). On the other hand, the healing time in the India-Burma group was not reduced; in 69 individuals given antitoxin, the average was 48 days in contrast with 41 days among 28 individuals who did not receive antitoxin. It was also the impression in the India-Burma theater that better scars resulted in those treated with antitoxin, provided it was administered within 30, or better, within 12 days of onset. It is significant to note that of the 14 patients in the India-Burma group who were reclas-

sified or transferred to the Zone of Interior, none had had diphtheria antitoxin within 32 days after onset of the lesions. These statements are to be regarded as suggestive, rather than final, statistically proved conclusions. According to Livingood,[64] the most important factors in preventing complications, loss of man-days, and loss of life from cutaneous diphtheria are early diagnosis of the disease, prompt hospitalization, and administration of diphtheria antitoxin as soon as possible.

TABLE 44.—*Study of influence of antitoxin on incidence of complications in 103 patients with diphtheria, 20th General Hospital, India-Burma theater*

Complication	Antitoxin given within 32 days after onset (36 patients)	Antitoxin given 32 days after onset (36 patients)	No antitoxin given (31 patients)
Neuritis	6	10	17
Neuritis and probable myocarditis	----	1	----
Neuritis and myocarditis	----	----	2
Myocarditis, probable	1	----	----
Myocarditis, acute, severe	----	----	1
Percent patients with complications	19. 4	30. 6	64. 5

NOTE.—Most of the men who received no antitoxin, or who received it late in the course of the disease, had the more severe lesions. Therefore, the results recorded in the table must be viewed with caution.

Local treatment.—The most important principles in healing the ulcers seen in the South and Southwest Pacific and in Burma seem to have been bed rest and the application of moist dressings. Outpatient treatment results in the lesions remaining unhealed for many weeks and continuing as a prolific source of diphtheria bacilli. Although *C. diphtheriae* is sensitive in vitro to sulfonamides, in ulcers it seemed to be almost unaffected by these drugs. In many instances in the South Pacific, the organisms were cultured directly from lesions packed with crystals or covered with sulfonamide ointment. Application of sulfonamides, however, gave the lesions a cleaner appearance.

Penicillin, locally applied in concentration of 250 units per cubic centimeter in physiological saline, has certain very definite indications that became evident during the course of a series of controlled observations in the South Pacific Area on Schick-negative individuals whose lesions contained toxigenic bacilli. The actual healing time of the ulcers was not significantly reduced. Results of treatment of lesions containing toxigenic *C. diphtheriae* in Schick-negative individuals are shown, as follows:

Type of treatment	*Number of patients*	*Mean healing time (days)*
Local, exclusive of penicillin	27	18.6
Penicillin soaks	43	16.5

64 See footnote 12 (4), p. 281.

In the India-Burma experience, penicillin seemed to give more initial improvement and afforded more relief from pain, but after 2 weeks its effect was not superior to those of other measures. Nevertheless, in the South Pacific, in each of six instances where an ulcer treated locally with penicillin was compared bacteriologically with a saline-treated control in the same individual, it was found that the toxigenic bacilli invariably disappeared from the former within 48 hours after the application of penicillin, whereas, in the latter, they persisted until the lesion was almost healed. The observations at Harmon General Hospital were similar, pathogenic organisms being eliminated in cases treated parenterally with penicillin in an average of 4 days; in those treated with saline alone, only 25 percent were cleared of the organisms in an average period of 8 days. Penicillin reduced not only the hazard of long contact with *C. diphtheriae* to the patient himself but to the community at large.

There seems to be some variation in resistance of diphtheria bacilli to penicillin, as emphasized by McDaniels.[65] His results indicating penicillin resistance of a majority of strains, however, are not in harmony with those of other observers, nor with the general clinical experience as summarized in the preceding section. McDaniels did not state the number of bacilli employed in his test, an important factor in determining resistance to inhibitory agents.

Surgical measures.—The experience of the India-Burma group indicated that operation should be considered if the ulcer fails to heal in 60 to 70 days. In diphtheritic ulcers a contracting scar was not formed; also, the thin new skin broke down once in every three patients. The most successful methods in a small group treated by Royster[66] seemed to be excision of the ulcer and a small margin of normal skin, followed by application of a split-thickness skin graft, rather than of the sliding flap, or extensive undermining and simple closure. The skin adjacent to the graft became more pliable. Skin grafts simply applied to large ulcers, even after they had begun to granulate cleanly, failed to take.

Factors in healing time.—If an atoxic organism was present, the healing time seemed to be significantly reduced. The following tabulation shows the relation of toxigenicity of *C. diphtheriae* to healing time in hospital:

C. diphtheriae	*Patients (number)*	*Mean healing time (days)*
Organisms toxigenic	107	19.2
Organisms atoxic	21	11.4

[65] McDaniels, H. E.: Penicillin Resistance of Diphtheria Bacilli. Mil. Surgeon 96: 95–96, January 1945.

[66] Royster, H. P.: Surgical Management of Cutaneous Postdiphtheritic Ulcers. Plast. & Reconstruc. Surg. 3: 294–302, May 1948.

Conclusions.—These observations suggest that the most efficient way of handling the patients is to put them at rest in bed and to apply penicillin locally in continuous soaks of 250 units per cubic centimeter. Most clinicians recommend the administration of antitoxin, at least if the individual is Schick positive. In retrospect, it would probably have been best to send only Schick-negative individuals into combat in the Tropics.

COST OF CUTANEOUS DIPHTHERIA TO THE ARMY

A substantial amount of disability was caused by cutaneous diphtheria during World War II. The lesions were present in all tropical areas, but the exact incidence is difficult to estimate. In the 35th Infantry, 25th Division, 6 weeks after evacuation from the New Georgia campaign, 19.4 percent of 200 men who were carefully questioned and examined had either active lesions or scars suggestive of previous infection with *C. diphtheriae.* Two of these were actually proved to have the organisms in their lesions. At the 54th General Hospital on Biak, 29 percent of admissions to the medical service were because of skin disease. It can be assumed that a considerable proportion of this was of diphtheritic etiology. In the South Pacific Base Command between 1 January and 30 June 1944, skin disease was the primary diagnosis of 9 percent of all medical evacuations to the United States. Many of these skin cases that had been studied at the 39th General Hospital were proved to be diphtheritic.

Much of the disability was the result of the location of the lesions on the feet and other places likely to be injured, an obvious consequence of the fact that trauma was a factor in their causation.

In a followup study of 140 patients in the India-Burma series, a total of 18,783 man-days were lost, an average of 4½ months per man, not including the days lost by 30 patients after their return to the Zone of Interior.[67] The total duration of skin lesions from appearance to healing averaged 91 days in another series in the India-Burma theater.[68]

The chief causes of prolonged hospitalization were breakdown of the thin scars when activity was resumed, or the neuritic or cardiac complications of the disease. In 53 of the 140 cases in the India-Burma group, the scars broke down upon resumption of activity and 13 of these showed no tendency to heal. This was the final result reported in August 1945. At the end of January 1945, in that group,[69] the causes of hospitalization in excess of 70 days in a total of 96 patients (69 percent of the total) were summarized, as follows:

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67 See footnote 13, p. 281.
68 See footnote 14, p. 281.
69 See footnote 12 (4), p. 281.

	Number
Neuritis	40
Indolent lesions	24
Recurrent lesions	23
Cardiac complications	4
Neuritis and definite cardiac complications in the same patient	3
Impetiginous eczema	2
Total	96

The total number of man-days lost in the 106 individuals on whom data are available in the South Pacific series was 2,077, an average of 19.6 days per man. The difference probably lies in the selection of cases. Probably only the more typical and severe cases were studied in Burma. This perhaps also accounts for the high incidence of neuritis in the India-Burma theater as compared with the South Pacific Area.

The followup study of the experience in the India-Burma theater showed that 60 percent of the men had returned to full duty; 18 percent had been reassigned, 12 of 25 because of cutaneous diphtheria alone; 22 percent had been returned to the Zone of Interior, 13 of 30 because of cutaneous diphtheria alone. It seemed, however, that prolonged inactivity occasioned by the cutaneous diphtheria had predisposed to the development of psychoneurosis which was listed as the primary diagnosis in some cases. When this is added to the followup study, the results are that 20 of 25 were reassigned and 22 of the 30 were returned to the Zone of Interior for causes ascribable to cutaneous diphtheria.

ROLE OF CUTANEOUS LESIONS IN THE SPREAD OF DIPHTHERIA

Evidence that Schick-positive individuals may infect the nasopharynx from their own cutaneous lesions has already been presented. Much evidence has accrued that ulcers can be a prolific source of diphtheria in others.

Evidence from contacts in hospitals.—In the late spring and summer of 1943 at the 39th General Hospital, in the South Pacific group, there were six instances of apparent contact infections among members of the staff or patients before tropical ulcers were recognized to be diphtheritic. A nurse attending an officer with widespread desquamative and ulcerative lesions had paronychia and an abscess in her arm from which *C. diphtheriae* and beta hemolytic streptococci were isolated. Another nurse attending the same patient contracted a sore throat which was not of membranous type. This nurse was known to have been Schick negative previously. Another officer, who had been admitted for jaundice 2 weeks before and who did not have a sore throat at the time of admission, was placed in the cubicle next to the first case and developed an extensive membranous nasopharyngeal diphtheria. A wardman on another ward, where many patients with tropical ulcers were kept, developed a paronychial granulomatous and ulcerative lesion from which the toxigenic corynebacteria were cultured (fig. 44), and shortly

thereafter another attendant on the same ward developed diphtheritic pharyngitis. Pharyngeal diphtheria developed in a wardman on another dermatology ward where there were many ulcer cases. All of these members of the hospital staff had been on wards caring for patients with cutaneous lesions. After isolation procedure was instituted for diphtheritic tropical ulcers, no other contact cases appeared except one in a nurse, attending an isolated patient with diphtheritic pharyngitis, who acquired a severe membranous nasal diphtheria. From all seven of these contact cases, virulent corynebacteria were isolated.

This experience in the South Pacific Area was not unique. In the India-Burma group,[70] 11 patients acquired cutaneous diphtheria after a period of hospitalization for another disease or injury. Faucial diphtheria developed in another patient in the 20th General Hospital 4 weeks after admission to the dermatology ward. Two of the patients with cutaneous diphtheria acquired pharyngitis and tonsillitis. In one patient, virulent organisms were isolated 3 weeks after admission, and in the other nontoxigenic bacilli were found 6 weeks after admission. Similarly, in a British experience in North Africa,[71] one nursing sister and one orderly in the dermatology ward contracted faucial diphtheria, and the medical officer in charge developed cutaneous diphtheria.

At the 13th General Hospital,[72] Finschhafen, two cases of diphtheria were recognized in the dermatology ward. Within the next 8 days, 7 clinical cases and 33 carriers were found by culture and were isolated, and in the following 7 days, 3 cases and 2 carriers were discovered. Seven patients in the dermatology section were found to be harboring the organism in skin lesions. The experiences at Lae, New Guinea, and at Hollandia were similar. In summary, then, beginning in the latter part of September 1944, cases of pharyngeal diphtheria appeared in wards devoted exclusively to dermatological cases and similar outbreaks centered around these wards.

At Harmon General Hospital,[73] a case of faucial diphtheria developed on a dermatology ward. The procedure described in the section on treatment and case findings was then instituted (p. 304). The results of culturing 42 patients and 11 attendants on the ward at the time the first case was discovered were that 10 were found to have *C. diphtheriae*, 2 of which were proved to be toxigenic. One of the patients with toxigenic organisms was a nurse.

At Letterman General Hospital,[74] eight cases of diphtheria originated in the dermatology section between 21 and 29 September 1944. The first four occurred in wardmen; the next two were in personnel of the physiotherapy section. All were of the pharyngeal type and were moderately

70 See footnote 12 (4), p. 281.
71 See footnote 7 (2), p. 279.
72 Essential Technical Medical Data, U.S. Army Forces in the Far East, for October 1944.
73 See footnote 18 (2), p. 282.
74 See footnote 20, p. 283.

severe except the first, which was fulminating, with hemorrhagic membrane. All organisms isolated were of the toxigenic *mitis* variety. Cultures of dust from the dermatology ward were found to contain *C. diphtheriae*, which was virulent for a guinea pig. The noses and throats of the patients and personnel of the dermatology and physiotherapy sections and in the castroom were also cultured and 14 were found to harbor toxigenic *C. diphtheriae*. Six of the fourteen were Schick positive. These observations emphasize the menace of unrecognized cutaneous diphtheria.

GENERAL CONSIDERATIONS OF DIPHTHERIA IN THE TROPICS

Diphtheria among the natives.—In the course of investigating the cutaneous diphtheria among the soldiers in the New Hebrides and later on Saipan, it was noted that the natives, particularly young children, had cutaneous lesions resembling those of the soldiers. Many of these were found to contain *C. diphtheriae*. Two of four Melanesian natives (figs. 43E and 45), one with apparently superinfected yaws, yielded atoxic *C. diphtheriae*. Six of fifty-three Tonkinese children had multiple punched-out lesions generally more superficial but like those observed in the soldiers (fig. 44). Four of these yielded organisms that had the morphological and biochemical characteristics of *C. diphtheriae* type *mitis* but were not toxigenic. Lesions of identical appearance were found in large numbers among Chamorro children on Saipan. Fifteen strains of *C. diphtheriae* type *mitis* derived from these were tested for toxigenicity and one was found to be toxigenic. It is of some interest to note, and not easy to explain, that some of these ulcers occurred in older children who were Schick negative. The lesions were most numerous where trauma was likely to occur, as about the knees, but they also were found elsewhere. Scars of such lesions were abundant in children more than 7 months of age, and they were almost universal above the age of 3 years.

Many studies have been made of Schick reactions of the natives in the Tropics. All have shown a high level of immunity. This has been found to be true among Filipinos, Malayans, Javanese, Hondurans, Brazilians, and the Bantu of Africa.[75] During World War II, in the British Army, the incidence of Schick-positive individuals among 900 sepoys was 1.1 percent, whereas among the British troops it was 27 percent.[76] In the South Pacific Area, the Schick reactions of natives more than 5 years of age were almost invariably negative in the Solomons (Melanesians), New Hebrides (Melanesians and Tonkinese indentured laborers and their families), and Saipan (Chamorros). Only between the ages of 7 months and 3 years was there a high incidence of Schick positives, in excess of 50 percent, among

[75] (1) Grasset, E.: Studies on Nature of Antidiphtheritic Immunity Among South African Bantu by Means of Schick Test and Antitoxin Titrations. South African M.J. 7: 779–785, 8 Dec. 1933. (2) Murray, J. F.: Diphtheria Amongst the Bantu. J. Hyg. 43: 159–169, September 1943.

[76] See footnote 1, p. 276.



FIGURE 44. Diphtheritic paronychiae. The patient was a wardman and, for several weeks, had attended an officer with lesions resembling those shown in figure 42. This was a contact case that occurred at the 39th General Hospital in New Zealand, 1943.



FIGURE 45. Toxigenic *Corynebacterium diphtheriae* in skin of palms and multiple paronychiae of 6 weeks' duration, acquired in the Solomon Islands. There was moist, desquamative dermatitis of the extremities with ulcer of leg.

the natives of the various races investigated. The theory was advanced for the first time, that the rapid reversal of Schick reaction was the result of immunization by the cutaneous route. It appears that the antitoxin level falls sufficiently to give a positive Schick reaction for only a short time, after loss of the transplacentally acquired immunity. This probably accounts for the rarity of severe nasopharyngeal diphtheria among natives of the Tropics.

Conditions among soldiers analogous to those of the natives.—It has been suggested that the same conditions which favor the establishment of the enormous reservoir of cutaneous diphtheria that has been demonstrated among the natives prevail also among soldiers in combat. These conditions are:

1. The warm, moist condition of the skin, which comes to resemble the pharynx.
2. The lack of facilities for washing.
3. The intimate crowding of the population.
4. The numerous opportunities for minor trauma produced mechanically or by insects.
5. The abundance of flies.

All of these conditions are extremely favorable for the spread of cutaneous diphtheria. Among the soldiers, where there are many individuals with low antitoxin titers, in contrast with the natives, there was a high incidence of nasopharyngeal as well as cutaneous infection. The barrier of cleanliness accounts for the fact that colonizers living in the Tropics under peacetime conditions are generally more susceptible than the natives, as indicated by the results of Schick tests, and that the former sometimes have nasopharyngeal diphtheria in epidemic form. One such epidemic is recorded by Fox and MacDonald (quoted by Forbes),[77] in a school at Shillong, Assam, the very region where tropical ulcers have been so common in natives as well as in U.S. soldiers.

The tropical environment in association with the dirt and crowding is the determining factor in the spread of the cutaneous varieties of diphtheria. The original source of *C. diphtheriae* is difficult to determine. Carriers are always present in our own population, and the native reservoir may at times be important.

ASSOCIATION OF CUTANEOUS AND NASOPHARYNGEAL DIPHTHERIA IN MILITARY UNITS IN THE TROPICS

As in the desert campaigns described so well by Bensted,[78] and Cameron and Muir,[79] nasopharyngeal diphtheria has been coexistent with, but usually

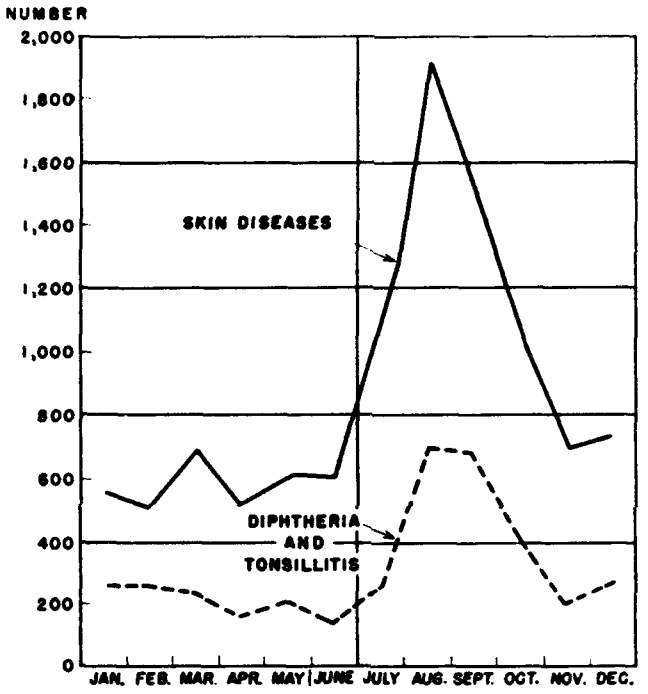
[77] Forbes, J. G.: The Prevention of Diphtheria. Special Report Series No. 115. London: His Majesty's Stationery Office, 1927.

[78] See footnote 41, p. 296.

[79] See footnote 42, p. 297.

has been exceeded in incidence by, cutaneous diphtheria. This was true again in British experience in the Mediterranean, in the South Pacific, and in the Southwest Pacific, although at the 20th and 69th General Hospitals in the India-Burma theater [80] relatively few nasopharyngeal cases were diagnosed. The course of the epidemic in the 27th Division while at the rest area in the New Hebrides is shown in table 45. The peak occurred on 23

CHART 14.—*Number of cases of skin diseases and diphtheria and tonsillitis in the* Afrika Korps, *1942*



September 1944. In this same group, 17 nasopharyngeal cases had previously been diagnosed on Saipan, shortly after the campaign on that island. In a more general way, the incidence of skin disease and diphtheria and tonsillitis was closely parallel also in the *Afrika Korps* (chart 14).

It will be noted in table 45 that, as the patients with ulcers were removed from the division by use of the outpatient clinic described previously, the incidence of nasopharyngeal diphtheria decreased rapidly. The course of the outbreaks was almost identical in the 25th and 43d Divisions previously studied in New Zealand.

Skin-to-skin contact seems the most usual method of the spread of the bacilli among the crowded combat troops in the Tropics. This is supported by the fact that in general the nasopharyngeal carrier rate among U.S. troops in the Tropics has been low. It was less than 1 percent among 800 men from two divisions tested in the South Pacific Area. In a series of 174 patients with ulcers, the incidence of asymptomatic carriers was 4 percent.

[80] See footnote 15, p. 281.

TABLE 45.—*Cases of diphtheria in the 27th Division in rest area in the New Hebrides, 16 September–28 October 1944*

Date of admission	Skin cases			Throat carrier	Throat case	Total
	Throat negative	Throat carrier	Throat case			
1944						
September 16	1	1	0	0	4	6
17	2	0	1	0	1	4
18	5	0	1	0	1	7
19	1	0	0	0	2	3
20	0	0	0	0	1	1
21	3	0	1	0	4	8
22	3	0	0	0	1	4
23	11	0	0	1	2	14
24	7	1	0	0	1	9
25	7	0	1	0	0	8
26	5	0	0	0	0	5
27	0	0	0	0	1	1
28	1	0	0	0	0	1
29	2	1	0	0	0	3
30	0	0	0	0	0	0
October 1	0	0	0	0	0	0
2	2	0	0	2	1	5
3	1	1	2	0	1	5
4	2	0	0	0	0	2
5	2	0	0	0	1	3
6	1	1	0	0	0	2
7	1	0	0	0	0	1
8	0	0	0	0	0	0
9	1	0	0	0	2	3
10	0	0	0	0	0	0
11	3	0	0	0	0	3
12	1	0	0	0	0	1
13	1	1	0	0	1	3
14	0	0	0	0	1	1
15	0	0	0	0	0	0
16	1	0	0	0	1	2
17	1	0	0	0	1	2
18	1	0	0	0	1	2
19	3	0	0	0	0	3
20	0	0	0	0	0	0
21	0	0	0	0	0	0
22	0	0	0	0	0	0
23	2	0	0	0	0	2
24	1	0	0	0	0	1
25	0	0	0	0	0	0
26	1	0	0	0	0	1
27	1	0	0	0	0	1
28	3	0	0	0	0	3
Total	77	6	6	3	28	120

The one group in which the carrier rate has been extremely high in the absence of clinical diphtheria was among German prisoners of war [81] at the camp in Merano. Here, it was 17 percent in apparently healthy individuals in a camp where there were many cases of neuritis. This carrier rate was exceeded only in convalescents from clinical diphtheria at the same camp. Evidence has been presented that diphtheria can be spread not only from skin to skin but also from skin to pharynx and from pharynx to skin. The same or other individuals can be involved in this process.

Other factors were considered in Burma. Investigators cultured rice paddies as possible sources of *C. diphtheriae* among soldiers in the Myitkyina area but found them to be negative.[82] Flies, in places where cutaneous diphtheria was prevalent, were cultured in the Southwest Pacific Area.[83] They were found to harbor *C. diphtheriae* on several occasions, but all strains were atoxic. The role of flies certainly deserves further study, since their known persistence and the attraction which the ulcers seem to have for them possibly may make them important in spreading the organism in the Tropics.

DIPHTHERIA TRANSMITTED FROM MILITARY TO CIVILIAN POPULATIONS

There is some evidence suggesting that tropically acquired cutaneous diphtheria in soldiers may ultimately be the source of infection to much larger susceptible civilian populations in temperate climates where it takes the nasopharyngeal form. The evidence may be summarized, as follows:

1. Cutaneous diphtheria is frequently ignored by the soldier and often escapes undiagnosed by his physician. Consequently, when the soldier returns from tropical combat to contact with civilians, his movements are unrestricted, and there is excellent opportunity for the dissemination of bacilli in the often rich secretions of the diphtheritic lesions of the skin.

A specific example is cited in a case investigated by the New York State Department of Health. The following is quoted from a letter from Dr. Hollis S. Ingraham, Chief, Division of Communicable Diseases:

> An Army captain had been hospitalized in New Britain [Bismarck Archipelago] in February 1944, for cutaneous ulcers of the legs, buttocks, and hand. He was returned to this country and was again hospitalized at Fort Dix, [N.J.] in June 1945. He visited at his home in Hornell, N.Y., from July 27 to August 10, 1945. At the time, there was still a deep ulceration on his left hand and arm. A son born in the household on July 26 was circumcised on July 31. This child was noted to be ill on August 18 and on inspection, the circumcision wound was found to be unhealed and covered with a diphtheritic membrane. Virulent diphtheria bacilli were recovered from the wound, and the child responded to specific therapy.
>
> An adult female, the captain's wife, developed sore throat on 24 August. Virulent diphtheria organisms were found in her throat and she responded promptly to antitoxin.

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[81] See footnote 23, p. 283.

[82] Letter, Maj. J. L. Arbogast, MC, 9th Medical Service Detachment (Laboratory), to Commanding Officer, 9th Medical Service Detachment (Laboratory), 16 Nov. 1944, subject: Diphtheria Survey.

[83] See footnote 16, p. 282.

A 7-year-old boy, another son, developed mild diphtheria on August 30 and responded promptly to treatment. Virulent diphtheria organisms were recovered from his throat. The captain developed no sore throat and there was no mention of any change in the ulcers on the left hand and arm. It was reported that a culture taken from his hand on August 23, 1945 at Fort Dix was negative. These lesions were cultured in Hornell on September 6, and pure culture of diphtheria organisms were recovered. On the whole, it appears highly probable that the infection was introduced by the captain but, as you will note from the dates, the case was not proved beyond doubt.

2. The return of infected soldiers has in some countries been associated with a striking increase in diphtheria among the civilian population. This occurred in Germany and certain occupied countries, and also in New Zealand.

Diphtheria had a high incidence in the summer months of 1941 and 1942 in the *Afrika Korps*, and in each year it waned during the fall and winter months. This information is derived from captured German documents in the European Order-of-Battle Section, G–2, Headquarters, Army Ground Forces. The epidemic began late in July 1941. In September, there were 416 diagnosed cases, largely in the *21st Panzer Division*, but there were some also in the *15th Panzer Division*.[84] In the report of the chief surgeon of the *Panzer Army* in 1941, the following statement appears (translated):[85] "There were four outstanding diseases, which in increasing measure had an uncommonly high incidence: Dysentery, jaundice (infectious icterus), diphtheria, and ulcers of the skin, especially of the lower extremities." In the next year, the table of incidence taken from the corresponding report, is very similar (chart 14). Diphtheria of the skin among German soldiers was reported in several papers in *Der deutsche Militärarzt*.[86]

One such outbreak in the United States was carefully studied by Fleck, Kellam, and Klippen.

The high carrier rate in the prisoner-of-war camp at Merano and the associated diphtheria there have been discussed previously. The evacuation of Germans from the North African campaign was progressing continuously in 1941 by hospital ship to Naples, Italy, thence by train to Germany, where Munich was the usual debarkation point. From April to December 1941, 8,400 were sent from Italy to Germany by train.

Diphtheria underwent a sudden and simultaneous increase among the civilian populations in Germany, Norway, and the Netherlands in Septem-

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84 Deutsches Afrika Korps. Tätigkeitsbericht der Abt. IVb, 30 Sept. 1941. [Captured German document.]

85 Armeearzt, Hauptquartier Panzerarmee Afrika. Erfahrungsbericht, 28 Feb. 1942. [Captured German document.]

86 (1) Binhold, (NFI): Über Wundiphtherie. Deut. Militärarzt 8: 521–527, September 1943. (2) Funk, C. F.: Die chronisch-ulcerosen flächenhaften Pyodermien: Ecthyma simplex. Pyodermia papillaris vegetans et exulcerans, sowie das Ulcus cruris ohne Ulcus varicosum. Deut. Militärarzt 9: 401–404, September 1944. (3) Quartiermeister (Rom) IVb, Zurzer Tätigkeitsund Erfahrungsbericht für die Zeit von 6.2.1941 bis 31.12.1941 des Danitätssoffz. bei QM. Rom (Heer). Sect. VI. Abtransport Verwundeter und Kranker der Panzergruppe Afrika, 28 Jan. 1942. [Captured German document.]

ber 1941 (chart 15), at the same time the diphtheria epidemic was at its height among the German soldiers in North Africa and while troops were being continually evacuated from that theater. In France, the increase occurred largely in the northern, occupied parts of the country.[87] It was not until after a considerable interval of time that the disease became prevalent in neutral countries, such as Sweden and Switzerland, to which travel from Germany was relatively slight (chart 16).

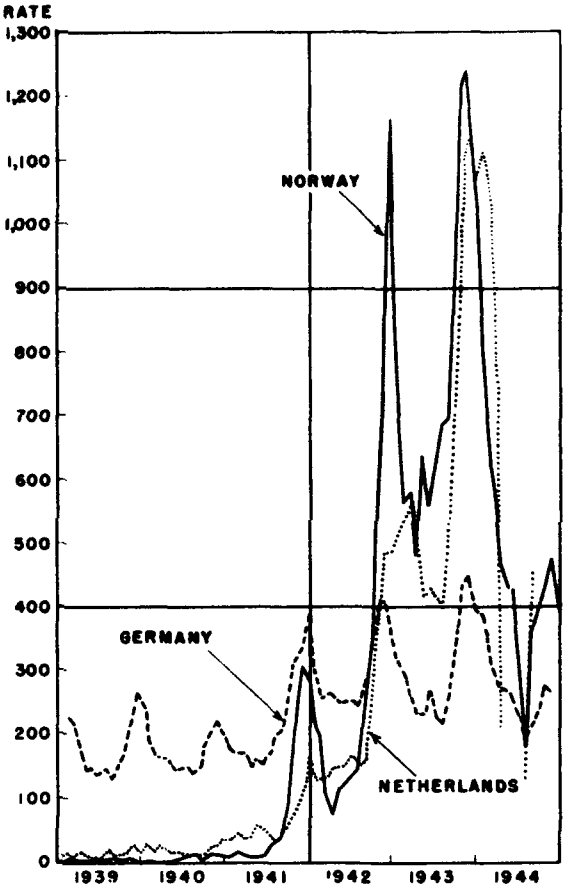


CHART 15.—*Diphtheria in Germany, Norway, and the Netherlands, 1939–44*

[Rate expressed as number of cases per annum per 100,000 population]

Source: Charted from data in League of Nations, Health Section of the Secretariat, Weekly Epidemiological Record.

It may be objected that dietary conditions in these countries were poor. However, a similar increase in incidence of diphtheria occurred in New Zealand where the diet was more than adequate. Here, it was associated, at least in time, with the return of U.S. Marines and later U.S. Army troops from campaigns in the Solomon Islands. Diphtheria among the Marines has been described by Norris and others. The influx into the country began after the middle of 1942. The 25th Division appeared en masse in New Zealand in 1943; the 43d Division arrived later. Diphtheria among these soldiers is described in detail in this chapter. Thus, the stream of individuals infected with *C. diphtheriae* had been uninterrupted until the middle of

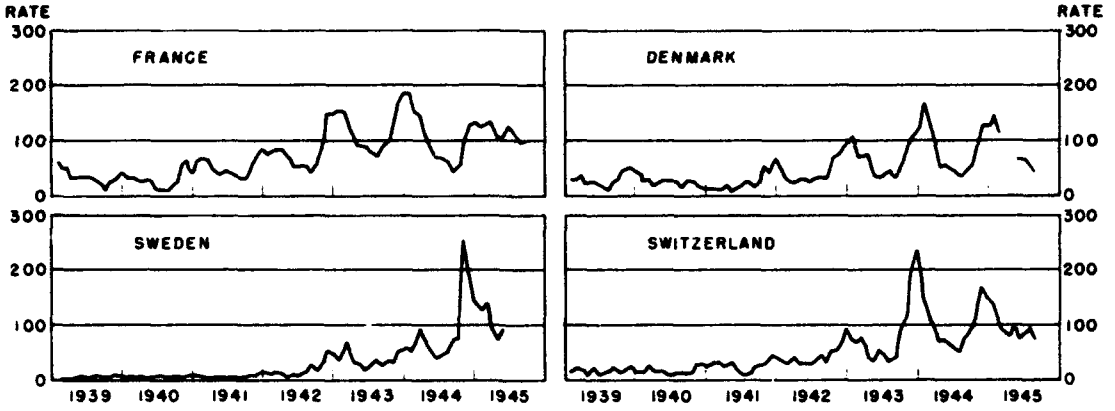
[87] Stowman, K.: Diphtheria Rebounds. Epidemiol. Inform. Bull. 1: 157–168, 28 Feb. 1945.

1944. Therefore, the morbidity from diphtheria in the New Zealand civilian population as of 1940–41, with the rise which began in 1942 is as follows:

	Number
1940	368
1941	383
1942	643
1943	830

CHART 16.—*Diphtheria in France, Denmark, Sweden, and Switzerland, 1939–45*

[Rate expressed as number of cases per annum per 100,000 population]



Source: Charted from data in League of Nations, Health Section of the Secretariat, Weekly Epidemiological Record.

The previous peak in New Zealand was in 1917–18 and may have been associated with the return of soldiers at that time from Gallipoli and the Desert.

It is of interest that the great pandemics of previous centuries appear to have come from the South.[88] According to Friederich Löffler, quoted by Nuttall,[89] "The disease appears to have been perfectly well known in Egypt, Syria, and Palestine even in ancient times. This is proved by repeated references to it in the Babylonian Talmud." Also, according to Rolleston,[90] in the first century A.D., "an unmistakable description of diphtheria is given by Aretaeus of Cappadocia under the name of Syriac or Egyptian ulcers owing to its having originated in Syria and Egypt whence it spread to all European countries." The "ulcers" refer to the appearance of the throat and not to the skin in this instance.

These correlations are not held up as final proof of the importance of cutaneous diphtheria among the military as the ultimate source of the epidemic in Europe. However, as Rolleston says: "Subjects of clandestine diphtheria, like clandestine prostitutes, are of considerable epidemiological

[88] Russell, W. T.: The Epidemiology of Diphtheria During the Last 40 Years. Special Report Series No. 247. London: His Majesty's Stationery Office, 1943.

[89] Nuttall, G. H. F., and Graham-Smith, G. S.: The Bacteriology of Diphtheria. Oxford: Cambridge University Press, 1908.

[90] Rolleston, J. D.: Acute Infectious Diseases. London: William Heinemann, Ltd., 1925.

importance as both, owing to their innocent appearance, may widely spread disease before their true nature is recognized." Streptococci may be similarly introduced since they abound in cutaneous lesions in the Tropics.

Part III. A New Hemolytic Corynebacterium in Man

A hemolytic corynebacterium was frequently cultivated from nasopharyngeal and cutaneous infections in soldiers evacuated from tropical islands of the Pacific and from natives of the New Hebrides and the Marianas. This organism which was given the tentative designation "*Corynebacterium hemolyticum*" is similar to a large group[91] of hemolytic corynebacteria, such as *C. ovis* and *C. pyogenes*, known to be pathogenic for animals. This organism is important because:

1. It may readily be confused with *C. diphtheriae* in direct smears of exudates and on Löffler's slants, and with beta hemolytic streptococci on blood-agar plates.

2. There is suggestive evidence of its pathogenicity for man. In smears of exudates and Löffler's slants, the new organism closely resembles *C. diphtheriae*, although it tends to be more slender. It is pleomorphic and granular, but the granules are not metachromatic. On filtered sugar media enriched with human serum (serum or blood is necessary for abundant growth), sucrose is fermented without the production of gas, as are also dextrose, maltose, lactose, galactose, and dextrin, but not xylose or mannitose. *C. hemolyticum* also differs from *C. diphtheriae* in coagulating milk, in slowly liquefying gelatin, and in not reducing nitrates. When inoculated intracutaneously into guinea pigs or rabbits, *C. hemolyticum* produces lesions resembling those caused by *C. diphtheriae*, but these are not prevented by diphtheria antitoxin, in the standard virulence test of Fraser and Weld. *C. hemolyticum* produces hemolytic and skin necrotizing toxins in broth that will not pass the Seitz filter.

On 24-hour blood-agar plates (pH 7.4), the organism is more hemolytic than *C. diphtheriae* type *mitis*, and its colonies resemble those of the beta hemolytic streptococcus. When the plates are allowed to incubate for 48 to 72 hours the colonies of *C. hemolyticum* continue to grow and become discoid, contrary to those of the *Streptococcus*, and the zone of hemolysis becomes enormous, usually after passing through a double phase. Other colonial characteristics are a lenticular dark spot visible by transillumination and etching of the surface of the blood-agar plates. Both of these phenomena are manifest in colonies more than 24 hours old and are not seen with the beta hemolytic streptococcus (fig. 46–55).

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91 Brooks, R. F., and Hucker, G. J.: A Study of Certain Members of the Genus Corynebacterium. J. Bact. 48: 295–312, September 1944.

The pathogenicity of *C. hemolyticum* for man is indicated by its capacity for producing lesions when inoculated into the skin. Its low invasiveness, however, is inferred by the absence of complications after intracutaneous injections in man and by the failure of development of significant symptoms when sprayed on the normal throat. It readily becomes parasitic in

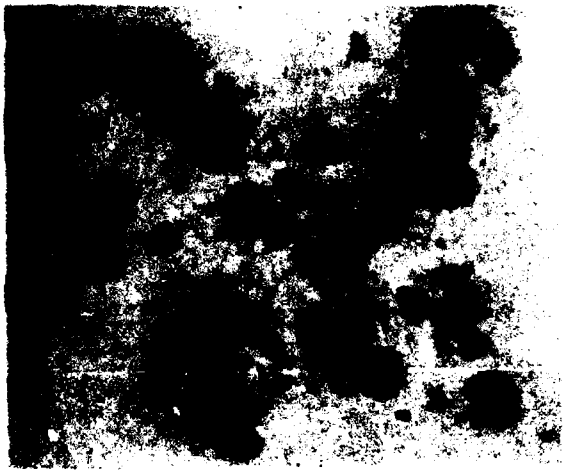


FIGURE 46.—Exudate from diphtheritic ulcer. *Corynebacterium diphtheriae* within the leukocytes. Irregular granular bacilli. Gram stain. (× 500)

the nasopharynx, where it may persist for many weeks. In conjunction with another infectious agent or a lowering of resistance of the host, however, it is possible that *C. hemolyticum* may become an "opportunist pathogen" for man. This is supported by the evidence of clinical cases in which *C. hemolyticum* was the dominant organism during the course of an acute respiratory illness, was unassociated with a known pathogen, and disappeared with the subsidence of the disease.



FIGURE 47.—Exudate from ulcer in one of the lesions depicted in figure 37A. Note double suppository forms of *Corynebacterium diphtheriae* sometimes observed in direct smears of exudate. (× 1,100)



U.S. Army photograph

FIGURE 48.—Chronic ulcer of ankle containing *Corynebacterium diphtheriae*. This condition was nontoxigenic in Melanesian native of Espíritu Santo, New Hebrides Islands.

Part IV. Use of Penicillin in Treatment of Diphtheria

Interest in penicillin as a possible therapeutic agent against diphtheria was high since it was known from earlier observations of the British that *C. diphtheriae* was sensitive to penicillin in vitro. Some evidence of variation in the susceptibility of various strains has been pointed out by McDaniels. In the European theater, investigation of the subject was stimulated by Administrative Memorandum No. 151, Office of the Chief Surgeon, dated 27 November 1944, outlining a tentative program for the observation of the efficacy of penicillin in the treatment of diphtheria.

All observers were agreed that following use of the drug in the active nasopharyngeal form of diphtheria there was often evidence of clinical improvement,[92] but some ascribed this to the effect on the frequently concomitant streptococcal infection. It soon became obvious by the review of fatalities and serious complications that penicillin, even when given early and abundantly, did not prevent myocarditis.[93] In the words of Colonel Middleton, Chief Consultant in Medicine, European theater:[94] "There is no substitute for antitoxin administration on suspicion without undue reliance

[92] Karelitz, S., Moloshok, R. E., and Wasserman, L. R.: Penicillin in the Treatment of Diphtheria and the Diphtheria Carrier State. ETO Med. Bull. 32: 67–72, July-August 1945.

[93] (1) See *footnote* 59, p. 302. (2) Berman, B. B., and Spitz, S. H.: Penicillin in Clinical Diphtheria. [Official record.]

[94] See footnote 35, p. 293.



FIGURE 89. Diphtheritic ulcers in children. A, Melanesian child in New Hebrides Islands with typical punched-out ulcers of the skin and yaws of the right foot. Ulcerative lesions in both instances contained nontoxigenic *Corynebacterium diphtheriae*. B, Tonkinese child, about 2 years old, with multiple ulcers. Some appear punched out; others are partly or completely scarred with bronze-violet pigmentation of surrounding skin. Atoxic *C. diphtheriae* was cultured from one of the lesions.

on the laboratory on the part of the clinician." Otherwise, by delaying specific treatment until laboratory identification is complete, the clinician may himself perpetrate a virulence test on Homo sapiens with irreversible effect.[95]

Penicillin seemed particularly promising for use in the treatment of carriers, and was given study in various quarters with somewhat diverse results. There was variation in the definition of carrier and in the methods of application and dosage of penicillin. Among the criteria for checking the results of these experiments should be consideration of (1) whether an adequate number of cases was used, (2) whether a check was made on the natural decline of the carrier state, and (3) whether the recurrence of organisms was tested.

For these reasons, the work of Karelitz and his coworkers must be considered inconclusive. Berman and Spitz[96] in each of 10 cases instilled 1 cc.

[95] See footnote 7 (35, p. 279).

[96] Berman, B. B., and Spitz, S. H.: Treatment of Diphtheria Carriers With Penicillin. Bull. U.S. Army M. Dept. 4: 87-91, July 1945.

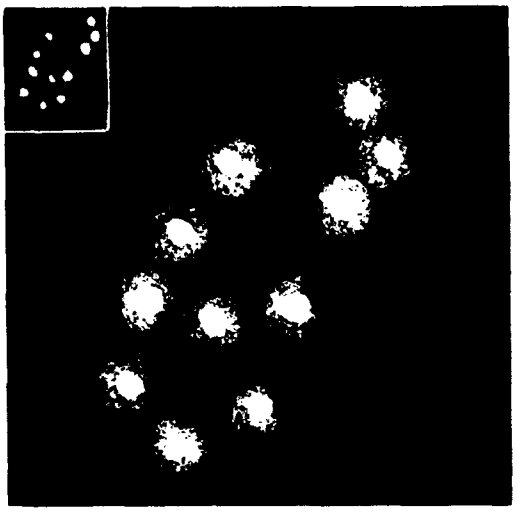


FIGURE 50. *Corynebacterium hemolyticum* colonies on blood agar from 18 to 24 hours. Hemolysis is beginning. (× 4) Inset shows actual size of colonies.

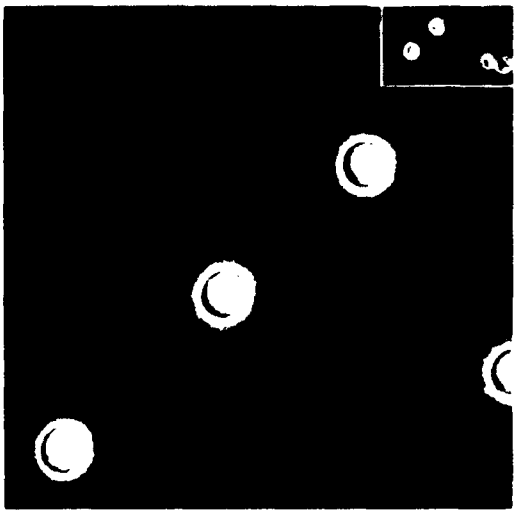


FIGURE 51. *Corynebacterium diphtheriae* 24 hours on 5 percent human blood agar, for contrast with *C. hemolyticum*. (× 4) Inset shows actual size.

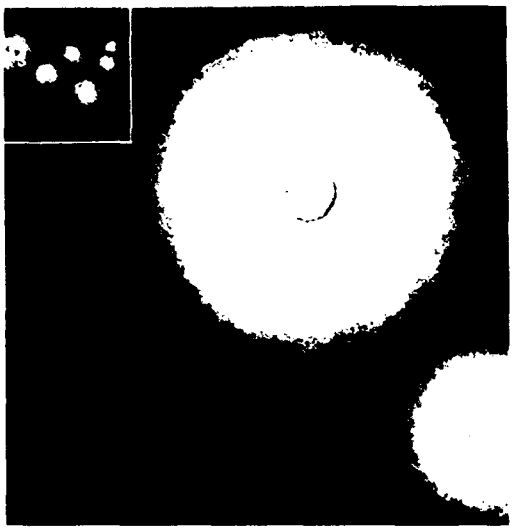


FIGURE 52. *Corynebacterium hemolyticum* 18 hours on 5 percent human blood agar contrasted with beta hemolytic streptococcus. Note greater translucency and less sharply defined border of *Streptococcus* colony. In the original, the latter has a silvery rather than pink color. Zone of hemolysis is now relatively smaller in contrast with appearance at 24 hours. Note minute pit at apex of *C. hemolyticum* colony. (× 4) Inset shows actual size of colony.

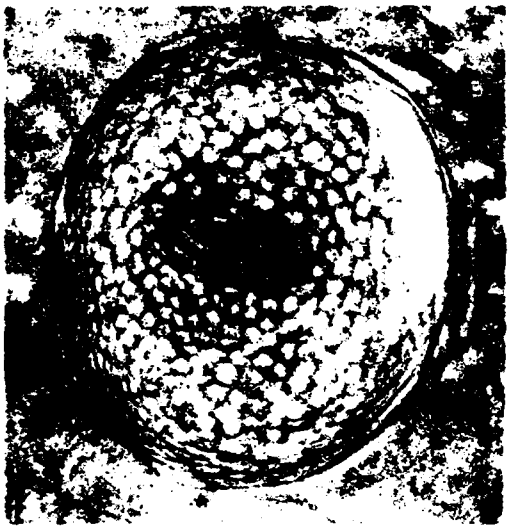


FIGURE 53. *Corynebacterium hemolyticum* colony 96-120 hours as seen under low-power, split lens of microscope. Note pebbled-leather appearance of surface of colony and lenticular opaque central mass. Light is partly transmitted and partly reflected from surface.

into each naris and the posterior pharynx four times each day for 5 days—a total of 20,000 units per patient for the 5-day period. Twelve controls had only hot gargles. All 10 penicillin-treated cases were negative within the treatment period or on the first day thereafter, and were still negative 4 weeks later. In the untested group, 7 of the 12 cases reverted spontaneously to negative within the fifth week. Berman and Spitz concluded that penicillin seemed useful, but the number of cases is small and the incidence of spontaeous reversals to negative was not checked 2 weeks after the treatment period when this might be at its height.

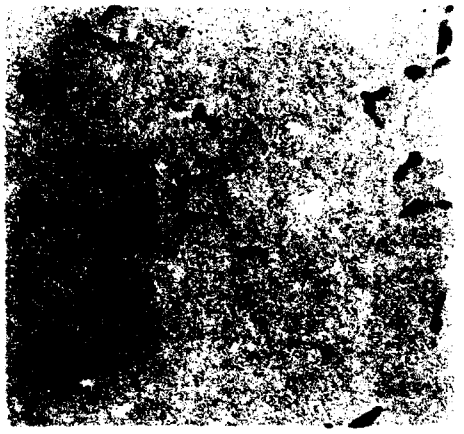


FIGURE 54.—*Corynebacterium hemolyticum*, 48 hours on Löffler's serum at 37° C. Gram stain. (× 1,100)

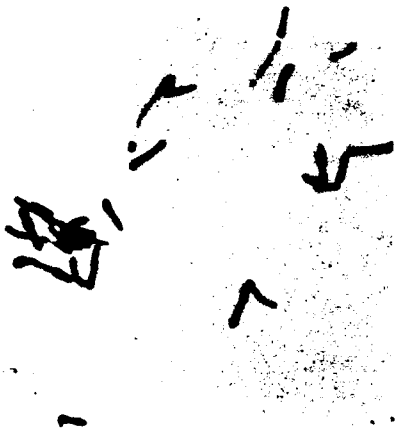


FIGURE 55.—*Corynebacterium diphtheriae*, 48 hours on Löffler's serum at 37° C. Gram stain. (× 1,100) (Compare with fig. 54.)

Bagnall and Bain[97] of the No. 14 Canadian General Hospital, in the Mediterranean, performed careful experiments using 175 patients and giving penicillin intramuscularly. Two groups were used: Group A received a total of 600,000 units in 5 days on a dosage schedule of 15,000 units every 3 hours; group B received a total of 1,200,000 units in 6 days on a schedule of 25,000 units every 3 hours. The percentage of success was higher in group B than in group A, which was no better than the control group. Bagnall and Bain pointed out that, in seven instances, positive cultures recurred after three consecutive negative cultures and in four instances, after four consecutive negative cultures. The writers' conclusions were that the results were disappointing.

Even less satisfactory were the results of intramuscular treatment of individuals who were still carriers 2 to 7 weeks after the clinical disease. Kocher and Siemsen[98] gave 25,000 units every 2 hours for 7 days, a total of 2,100,000 units. The cultures remained positive in their subjects.

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97 See footnote 1, p. 276.

98 Kocher, R. A., and Siemsen, W. J.: Diphtheria Carriers Treated With Penicillin. Ann. Int. Med. 24: 883-886, May 1946.

These observers concluded, however, on the basis of another experiment, that local therapy is effective. Their method was to use glycerine-gelatine lozenges, which required 20 to 30 minutes for solution, one each hour for 12 doses. The early patients in the series received lozenges containing 500 units, but their content was later raised to 1,000 units. Also, penicillin sprays to the nose were given. Twenty-three of thirty-one individuals cleared promptly in 1 to 10 days after treatment was started, and eight cases that were persistently positive had large tonsils. After tonsillectomy, however, these became consistently negative. Scrutiny of the table presented by these workers, however, shows that 10, rather than 8, cases must be considered failures. Furthermore, in seven others, the cultures were already negative before local treatment was started and are therefore "no test."

It still remains to be proved that penicillin is effective in terminating the carrier state. Certainly, it is much less effective in persistent carriers than tonsillectomy.

Part V. Problems Remaining for Investigation

Numerous problems have presented themselves during the course of these wartime investigations. They are, as follows:

1. Cutaneous diphtheria should be investigated among the natives of the New World Tropics. If the epidemiological factors are indeed the tropical environment in association with dirt and crowding, cutaneous diphtheria should be just as common in Haiti or Uganda as in Saipan. A study in relation to the rapid development of the immunity by performing antitoxin levels in natives in various age groups might be most revealing.

2. Of special interest would be an investigation of whether cutaneous diphtheria has a significant incidence in the poorer parts of the Southern United States where it may account for the high levels of Schick immunity observed there.

3. Further information should be gathered concerning the occurrence of cutaneous diphtheria in individuals previously Schick negative.

4. The suggestion from the observations of Pasricha and Panja that *C. diphtheriae*, which is not toxigenic for the guinea pig, may yet be capable of producing lesions in the human skin requires careful investigation. The factor of hypersensitivity may have significance in this connection.

5. Further study should be made of the newly described hemolytic corynebacterium of the *C. pyogenes* group in regard to its distribution among the peoples of the Tropics and its pathogenicity and origin, which may be in some species of animal.

6. Sufficient evidence in controlled experiments has not as yet been gathered concerning the efficiency of penicillin in treating the carrier state. Further investigation is highly indicated.

7. It was found that beta hemolytic streptococci were extremely common in cutaneous lesions of the natives. These should be investigated by typing and also in relation to the Dick reaction. A good deal may be learned concerning the actual prevalence of streptococci in the Tropics, contrary to previous opinions of their rarity in these regions.

Part VI. Summary

Diphtheria was a problem of increasing importance to the Army during World War II, particularly after the occupation of Germany. Many cases originated in the Tropics where the disease largely took the cutaneous form, as it has in previous tropical campaigns.

The lesions, which usually were preceded by trauma or insect bites, most commonly assumed the form of punched-out ulcers with declivitous margins and relatively clean bases, to which occasionally a grey-green membrane or fibrinous crust was adherent. The borders were usually indurated and blue or bronze violet in appearance. Exanthematous or moist desquamative lesions of entirely different appearance could, however, harbor large numbers of *C. diphtheriae.*

The complication of neuritis or myocarditis occurred occasionally, or in some groups of cases frequently, but usually there were no general symptoms of intoxication.

Aside from these complications, the lesions were important for:

1. The ulcers were usually on the extremities where they reduced the military efficiency of the soldier.

2. It is possible for a susceptible individual to infect his own nasopharynx.

3. The lesions, when unrecognized, can be a prolific source of both cutaneous and nasopharyngeal diphtheria for others. This is demonstrated by evidence of spread of diphtheria from patients on dermatology wards to other patients and to ward personnel; concomitance of nasopharyngeal and cutaneous diphtheria in military populations in the Tropics; and suggestive evidence that unrecognized cutaneous diphtheria in Rommel's soldiers was responsible for the epidemic in Europe where, on account of climatic conditions, the diphtheria took the respiratory form. The epidemic in Europe began in September 1941, when both cutaneous and nasopharyngeal diphtheria was at its height in the *Afrika Korps* and while large numbers of German soldiers were being returned to Germany as patients. It involved first those countries under direct occupation by the Germans and the neutral countries not until much later.

The conditions favoring the cutaneous localization of *C. diphtheriae* under conditions of combat in the Tropics are:

1. The warmth and moistness of the skin which comes to resemble the lining of the pharynx.

2. During combat, there is little opportunity for cleanliness.
3. Many minor infections occur and are neglected.
4. Flies are extremely numerous and travel from skin to skin.
5. There is frequent and extreme crowding of the troops.

These same conditions prevail among the natives in the Tropics, who constitute a tremendous reservoir of *C. diphtheriae*. Among them, cutaneous diphtheria is universal by the fourth year of age. Only between the ages of 9 and 24 months is there a high incidence of Schick-positive reactions among these people. Immunization by the cutaneous route probably accounts for the rapid conversion to the Schick-negative state. The level of immunity is probably only slightly depressed during this brief interval of time, and this probably accounts for the low incidence of nasopharyngeal diphtheria.

When the susceptible soldiers are forced by the vicissitudes of combat in the Tropics into the same epidemiological conditions as the natives, then severe faucial as well as the more common cutaneous forms of diphtheria become widespread.

The best treatment for cutaneous diphtheria appears to be to put the patient at rest in bed and to apply penicillin locally in continuous, moist saline compresses. Diphtheria antitoxin intramuscularly may prevent the consequences of autoinfection of the pharynx and possibly may diminish the incidence of complications.

The best measure of prevention of a cutaneous diphtheria is to send only Schick-negative troops into combat in the Tropics. The fact that more individuals who have diphtheritic ulcers are Schick positive than the general population, suggests that the Schick-negative state is, at least to some extent, protection against the development of the tropical ulcers.

In both cutaneous and nasopharyngeal infections in the Tropics, hemolytic corynebacteria are common which may resemble *C. diphtheriae* in direct smears and on Löffler's media. These require further investigation.

More study is necessary concerning the use of penicillin in terminating the carrier state and in the therapy of clinical nasopharyngeal diphtheria. Penicillin alone, even when given early and abundantly, does not prevent the complications of the disease.

CHAPTER XI

Tuberculosis

Esmond R. Long, M.D.

Part I. Tuberculosis in the Army

HISTORICAL PERSPECTIVE

For centuries, tuberculosis has been a principal cause of death in men of military age. In the 4-year period 1942–45, pulmonary tuberculosis, although steadily declining in prevalence throughout the country, was still the chief cause of disease death in the United States in men between the ages of 15 and 35 years. In most countries of the world, the relative importance of tuberculosis was much greater than in the United States. In all armies in all countries, whenever accurate records have been kept, it has proved to be a leading cause of disability, adding appreciably to the noneffective rate, making disproportionate demands upon the time and effort of medical officers as well as upon hospital and transport facilities needed for other diseases and for battle casualties.

The U.S. Army has maintained records of hospital admissions and military discharges for tuberculosis since the Civil War. An account of this disease as a military problem appeared in the "Medical and Surgical History of the War of the Rebellion" (pt. III, vol. I, Medical History) prepared under the direction of The Surgeon General and published in 1888. During nearly 5⅙ years of military mobilization and operation, 13,499 admissions for consumption and 5,286 deaths in white soldiers were reported. As calculated from these figures, the admission rate was 5.7 and the mortality rate was 2.2 per 1,000 per annum (table 46). In view of the relatively limited diagnostic facilities of the period, it is reasonable to suppose that the actual incidence was very much higher. As a matter of fact the reporting itself was at fault, for the figures for discharge are higher than the number of hospital admissions for consumption. The records indicate that 20,403 white soldiers were discharged because of this disease, an excess of 12,190 over the admissions, and this figure does not include those who died of consumption. The reasons for the discrepancy are complex, involving multiple causes of disability and the return of consumption cases to duty. The mean annual rate of discharge for consumption in the Army in the Civil War, calculated from the figures given in the "Medical and Surgical History of the War of the Rebellion," was 8.6 per 1,000 for white soldiers and 3.1 per 1,000 for Negro troops.

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TABLE 46.—*Admissions, deaths, and disability separations due to tubercular diseases in the U.S. Army (Union only), by diagnosis and race, May 1861–June 1866* [1]

[Rate expressed as number per annum per 1,000 average strength]

Diagnosis and race	Admissions		Deaths		Disability separations	
	Number	Rate	Number	Rate	Number	Rate
Consumption:						
White	13, 499	5. 67	5, 286	2. 23	20, 403	8. 58
Negro	1, 331	6. 94	1, 211	6. 32	592	3. 08
Total	14, 830	5. 77	6, 497	2. 53	20, 995	8. 17
Scrofula:						
White	6, 022	2. 53	99	0. 04	907	0. 38
Negro	2, 508	13. 08	81	. 42	147	. 77
Total	8, 530	3. 32	180	0. 07	1, 054	0. 41
Other tubercular diseases:						
White	369	0. 16	33	0. 01	.....	0
Negro	20	. 10	4	. 02	.....	0
Total	389	0. 15	37	0. 01	.....	0
Total tubercular diseases:						
White	19, 890	8. 36	5, 418	2. 28	21, 310	8. 96
Negro	3, 859	20. 12	1, 296	6. 76	739	3. 85
Total	23, 749	9. 24	6, 714	2. 61	22, 049	8. 58

[1] Data for Negro troops are for the period, July 1863–June 1866; there were no Negro troops prior to July 1863 in the Union Army.

Source: The Medical and Surgical History of the War of the Rebellion. Medical History. Washington: Government Printing Office 1875, pt. I, vol. I, pp. 636–637, 646, 710, and 716.

In the short Spanish-American War moderately high rates were recorded. For the decade preceding hostilities the average admission rate in the Army was 2.7 per 1,000 per annum, but in 1898, following accelerated enlistment and the call of the National Guard to service, it rose to 3.7, and in the following year reached 4.0.

In neither the Civil War nor the Spanish-American War, however, was tuberculosis considered of sufficient moment to call for unusual comment in the recorded analyses of the medical aspect of military operations. It was entirely different in World War I. The French Army recorded a great increase in the incidence of pulmonary tuberculosis during the first 5 months, especially in French prisoners returned from Germany. The French experience was sufficiently striking to engage the prompt attention of American authorities, who set up special machinery for the control of tuberculosis in

the U.S. Army. These procedures have been described at length by Col. George E. Bushnell, MC, and Col. Esmond R. Long, MC.[1]

Following demobilization, the incidence of tuberculosis in the U.S. Army decreased continuously for 20 years. The incidence rate was 4.6 per 1,000 troops per annum in 1920 and 1.4 in 1940. General improvement in measures for the control of tuberculosis in the Army, and a steady decrease in tuberculosis in the population were largely responsible for this decline.

DISCOVERY OF TUBERCULOSIS BEFORE INDUCTION

The magnitude of the tuberculosis problem in the Army in World War II, although substantial in the aggregate, was relatively much less than in any previous conflict. To begin with, a smaller proportion of men eligible for induction were tuberculous. In 1917, the national death rate from this disease was approximately 140 per 100,000 population. In 1941, it was less than one-third of that, or 45 per 100,000 population. The rejection ratio for tuberculosis, all forms, actual or suspected, among men examined at camps and by local boards during World War I was 2.3 percent. Nearly 3.8 million men were examined during World War I.[2] Even with the much superior diagnostic facilities of the Army in the Second World War, the rejection rate was much lower from the onset, averaging less than 1 percent for the entire period of mobilization.[3]

In World War I, the detection and exclusion from military service of men with tuberculosis were based almost entirely on the results of physical examination. Roentgenology was in its infancy, and only a few thousand soldiers were examined by X-ray. All experience since that time has indicated that physical diagnosis by even the most skillful, is much inferior to the roentgenographic methods in use at present. During the total course of mobilization for World War II, not less than 20 million men were examined roentgenographically in the Army enlistment stations and in the joint Army-Navy induction stations. Colonel Bushnell's conclusion on the value of X-ray examination in World War I is striking in the light of subsequent developments. It was based on the work of Matson,[4] and reads: "As compared with the physical examination, the roentgenological examination, even when done by an expert, occupies a place of secondary importance in the diagnosis of tuberculosis of clinical significance." However, as Spillman[5]

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1 (1) The Medical Department of the United States Army in the World War. Washington: U.S. Government Printing Office, 1928, vol. IX, pp. 171-202. (2) Long, E. R.: The War and Tuberculosis. Am. Rev. Tuberc. 45: 616-636, June 1942. (3) Long, E. R.: Tuberculosis as a Military Problem. Am. Rev. Tuberc. 51: 489-504, June 1945.

2 Britten, R. H., and Perrott, G. St. J.: Summary of Physical Findings on Men Drafted in the World War. Pub. Health Rep. 56: 41-62, 10 Jan. 1941.

3 Medical Department, United States Army. Physical Standards in World War II. [In preparation.]

4 Matson, R. C.: The Elimination of Tuberculosis From the Army. Am. Rev. Tuberc. 4: 398-416, July 1920.

5 Spillman, R.: The Value of Radiography in Detecting Tuberculosis in Recruits. J.A.M.A. 115: 1371-1378, 19 Oct. 1940.

wrote, the chest specialists of those days are "not to be reproached for not having knowledge that came into existence only later, any more than the chief of the army air service in 1917 is to be reproached because more efficient planes are available now than then."

During World War I, there were 22,812 disability separations due to tuberculosis, or 5.52 separations per annum per 1,000 average strength. If related to the number of men who served in the Army during the First World War, the proportion would be about 0.56 percent. Tuberculosis was the leading cause of disability separation, accounting for 11.1 percent of the total (204,765) and 13.5 percent of separations due to disease (169,039).[6] In World War II for enlisted men, it was 13th in the list, accounting for only 1.9 percent of all discharges for disability from disease.[7]

The full magnitude of the tuberculosis problem incurred in World War I did not become evident until several years had passed. The postwar cost proved enormous. Goldberg[8] calculated that the approximate expenditure of the Veterans' Administration for service-connected tuberculosis, including hospitalization and pension costs, from the close of World War I through 1940 was $1,186,000,000. To this vast monetary expense must be added millions of dollars spent by the Army and the Navy on tuberculosis patients prior to their discharge. Admissions to veterans' hospitals totaled 293,761 for the years 1921 to 1940, inclusive.

The peak load for hospitalized tuberculosis beneficiaries was reached in 1922 when a total of 44,591 such patients were treated in Government hospitals at a cost of almost $30 million.[9] As early as 30 June 1922, 36,600 veterans, or 1 in 130 persons in the Army, had been granted compensation for service-connected tuberculosis.

At the beginning of the Second World War, it was resolved not to repeat the experience of the First World War. It was recognized that the earlier high admission rate was largely due to the acceptance of men who were already infected. In Colonel Bushnell's opinion, relatively few men developed fresh infection in the Army. It was clear to the Office of the Surgeon General that modern methods could be highly effective in excluding the early types of tuberculosis that escaped recognition during the mobilization of 1917. The reader is referred to the chapter on tuberculosis in another volume in the history of the Medical Department in World War II for the general procedures employed at induction stations, and for a picture of the enormous extent of preinduction examination by X-ray.[10] Other

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[6] The Medical Department of the United States Army in the World War. Washington: Government Printing Office, 1925, vol. XV, p. 2.

[7] Health of the Army, Office of the Surgeon General, vol. 1, 31 Aug. 1946.

[8] Goldberg, B.: Presidential Address: War and Tuberculosis. Dis. of Chest 7: 322–325, October 1941.

[9] Wolford, R. A.: The Tuberculosis Program of the Veterans Administration. M. Bull. V.A. 21: 127–135, October 1944.

[10] See footnote 3, p. 331.

sections of the chapter describe measures to prevent the development of tuberculosis within the Army.

It is obvious that, in an army well screened to exclude men with active tuberculosis, contagion among troops would be slight. However, it must be realized that not all tuberculosis is visible in chest films and that a certain amount of pulmonary and nonpulmonary tuberculosis may be expected to develop as a result of endogenous spread from undetected foci. The longer the war, the more cases would develop from such hidden foci, and also from fresh, exogenous infections. In the Second World War, the period of mobilization and of hostilities was more than twice as long as in the First World War. Hence, it will not be surprising if research ultimately shows that tuberculosis spreading from lesions not detectable at the time of mobilization, on the one hand, and from fresh infections, on the other, were together responsible for a considerably larger share of the total number of cases discovered in the Army in World War II than was believed to be the case in World War I.[11]

DISCOVERY OF TUBERCULOSIS IN THE ARMY

The general machinery for discovery of tuberculosis in soldiers after acceptance for service was the same as for any other chronic disease; it was discovered both on the basis of symptoms and as a result of routine examination for any cause. Cases manifested by symptoms were diagnosed at sick call as suspected tuberculosis and were then referred to the station hospital serving the post at which the call was made for necessary observation and further diagnostic procedures. All station hospitals were thus concerned with the diagnosis of tuberculosis. Not all station hospitals, however, included on their staffs medical personnel qualified to recognize tuberculosis of minimal extent or borderline activity. Doubtful cases were referred to general hospitals for followup and accurate observation.

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[11] Long, E. R., and Jablon, S.: Tuberculosis in the Army of the United States in World War II. An Epidemiological Study With an Evaluation of X-ray Screening. VA Medical Monograph. Washington: U.S. Government Printing Office, 1 May 1955.

Postwar epidemiological and statistical study based on adequate sampling of men discharged with and without tuberculosis disclosed that approximately half of the men discharged for tuberculosis had the disease in roentgenologically detectable form at the time of acceptance for service, the lesions having been overlooked through induction station errors. There was reason to believe that of the other half a part represented new infections acquired in army service and a part the breakdown of old lesions not detectable by X-ray examination. Since routine tuberculin tests were not made at the time of induction, it was impossible to distinguish between these two groups. This study, in which all the films were read independently by two roentgenologists, with subsequent checking by two others, also disclosed a significant degree of fallibility in single chest X-ray interpretations. Not only did the two roentgenologists fail frequently to agree with each other, but in numerous cases they also failed to agree with themselves on reading the same films after an interval of a few months. It is now recognized that such discrepancy is general experience. The paper cites other reports in which similar lack of agreement was recorded. (See also Long, E. R., Stein, S. C., and Henderson, H. J.: Experiences With Dual Reading of Chest Photoroentgenograms. U.S. Armed Forces M.J. 7: 493-515, April 1956.) In the latter study, actual trial was made of dual reading in three Armed Forces examining stations. Comparison of the readings by the roentgenologist of the station of origin of the films and the roentgenologist of another station showed considerable disagreement in interpretation.

In addition, a good many cases were discovered in the course of routine X-ray examinations. Not a few were found in men applying for admission to officer candidate schools or for a commission at the termination of study in these schools. Many were found also in routine examinations for special service, particularly in the Army Air Forces, where many men were reexamined.

Moreover, tuberculosis was sometimes discovered incidentally to other illness requiring roentgenographic study. In the course of the long series of epidemics of atypical pneumonia that occurred during World War II, vast numbers of roentgenograms were made of the chests of men with the symptoms of pneumonia. Not infrequently, shadows in the lung fields persisted after clearing of the consolidation due to pneumonia and were shown by subsequent examination to represent tuberculous infiltration. A high percentage of these infiltrations were found to be well-scarred lesions, but in an appreciable number the process proved to represent active tuberculosis, requiring continued hospitalization.

INCIDENCE AND DISCHARGE RATES

Incidence rates.—The average incidence rate in the First World War, approximately 12 cases of tuberculosis per 1,000 men per annum for the years 1917 and 1918, was ten times that for World War II, which averaged 1.2 per 1,000 per annum between Pearl Harbor Day (7 December 1941) and V–J Day (14 August 1945). (See chart 17.) Nevertheless, in spite of better diagnostic facilities and techniques in the second great conflict, from 10 to 15 men with active disease per 10,000 accepted escaped detection in induction stations and were taken into the Army.[12] Moreover, about a million men in World War II were inducted into the Army before roentgenograms of the chest were a routine requirement.

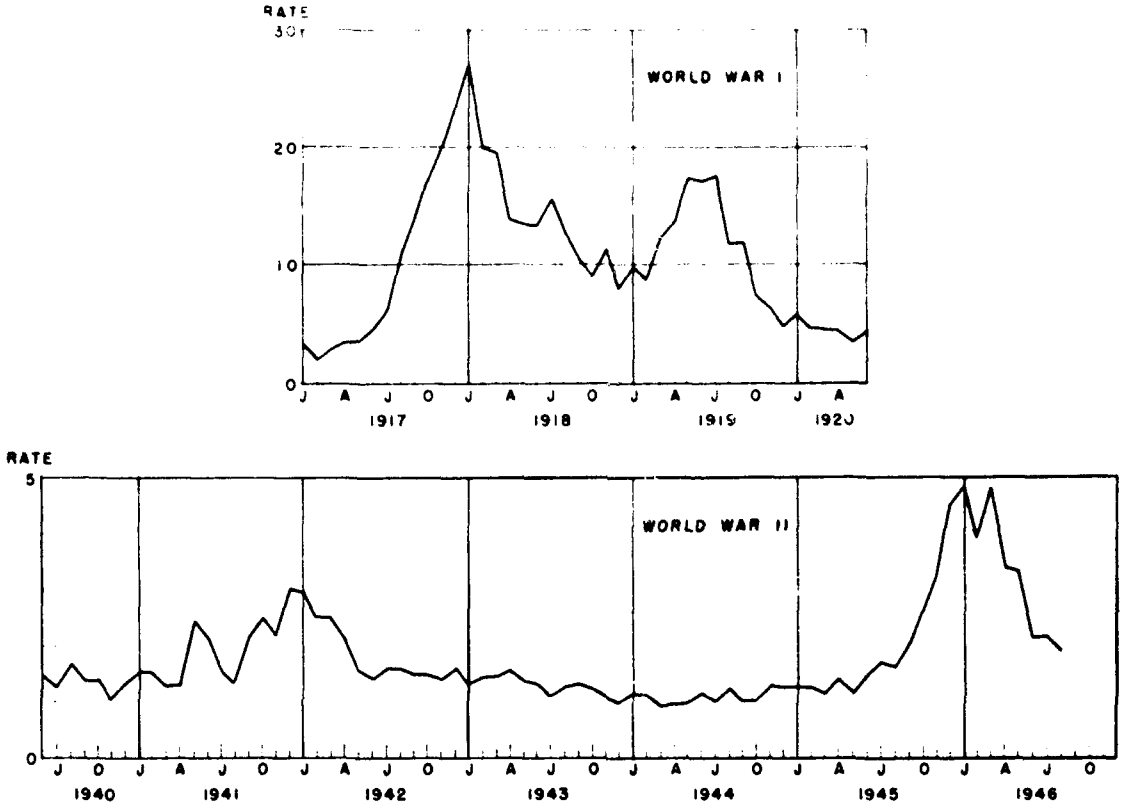
There is reason to believe that in each war a high percentage of the missed cases were discovered within a few months after induction. As a rule, although not invariably, symptoms soon became evident in advanced disease, leading to report at sick call, hospitalization, and diagnosis. This not greatly belated recognition of tuberculosis in recently inducted men is believed to account for a peculiarity common to the admission rate curves of the two wars. In the late months of 1917 and early months of 1918, the rate of admission to hospital was excessive as compared with that for the last half of 1918. A similar phenomenon occurred in the last half of 1941 and first half of 1942. It is believed that in each war imperfections in screening procedure were greater and more frequent at the outset than later in the course of mobilization and that an excessive number of men with disease that would soon become obvious were inducted at that time.

[12] Long, E. R., and Stearns, W. H.: Physical Examination at Induction. Standards With Respect to Tuberculosis and Their Application as Illustrated by a Review of 53,400 X-ray Films of Men in the Army of the United States. Radiology 41 : 144–150, August 1943.

A second characteristic of the two curves is a terminal rise. This rise represents discovery of cases on demobilization and is in part factitious. A number of cases per thousand that greatly exceeded the previous monthly average were discovered in the course of the physical examinations at discharge, which in World War II were as thorough as the induction examinations and included routine roentgenograms of the chest. The increased

CHART 17.—*Incidence of tuberculosis in the U.S. Army in the continental United States, World War I*[1] *and World War II*

[Rate expressed as number of cases per annum per 1,000 average strength]



[1] The World War I data are in terms of admissions and are limited to enlisted men.

Source: World War I—The Medical Department of the United States Army in the World War. Washington: Government Printing Office, 1925, vol. XV, pt. 2. World War II—Preliminary data based on periodic summary health reports, Office of the Surgeon General.

rate was artificially high because the strength of the Army from which it was calculated in accordance with conventional practice was continuously decreasing in size as a result of the process of demobilization.

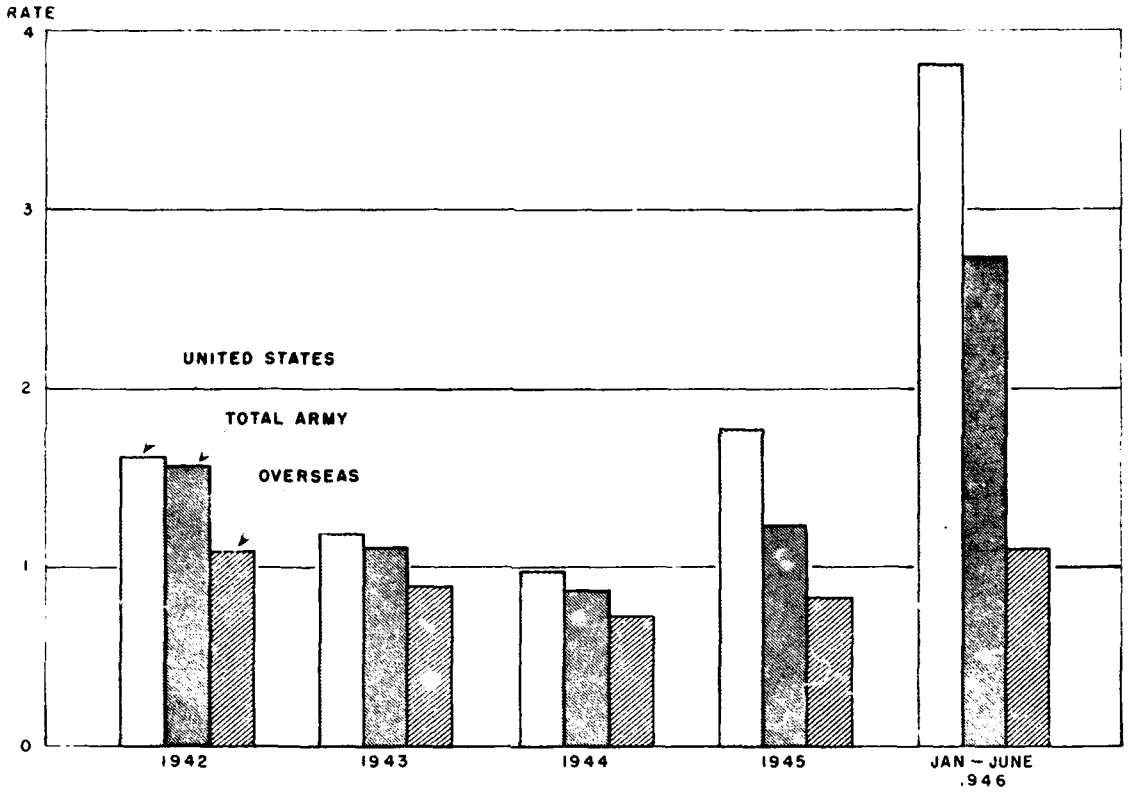
The admission rate was remarkable for its relative constancy over a period of 3 years from mid-1942 to mid-1945, inclusive. The rate of about 1 case per 1,000 troops per annum reflects the number of cases missed at induction stations, plus the number that developed from new infections during service in the Army. At the close of World War II, the necessary

research to determine the amount of previously existent but unrecognized tuberculosis, as compared with that developing in the absence of previously detectable disease, had not been accomplished.

The admission rates for the continental United States (chart 18) were higher than those for oversea theaters. This difference during the war might be attributed to the additional screening of troops through the rigors

CHART 18.—*Incidence of tuberculosis among U.S. Army troops in the United States and overseas, January 1942 to June 1946, inclusive*

[Preliminary data based on periodic summary health reports]
[Rate expressed as number of cases per annum per 1,000 average strength]



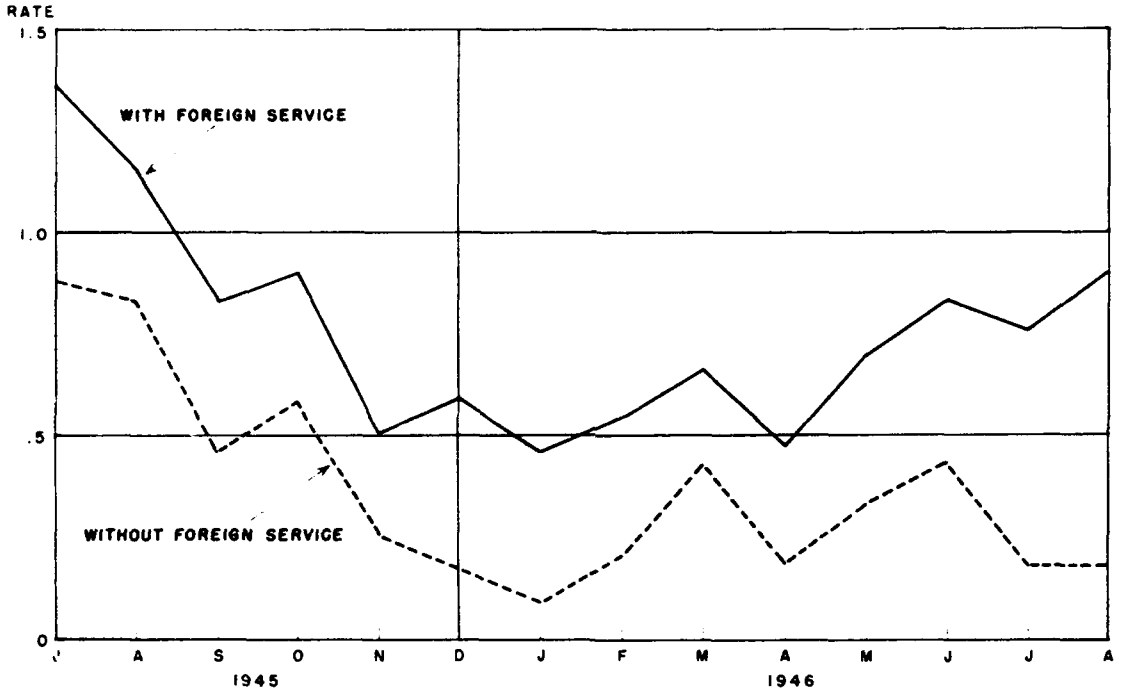
of basic training in the United States. The months of physically strenuous service, with daily sick call, and the frequent medical examinations for promotion or special service brought to light many men with tuberculosis, who were accordingly excluded from oversea assignment. Still more would have been excluded had it been possible to examine by X-ray all men leaving for foreign service. This was impossible because of limitations both of time and personnel, although there was a reasonably effective inspection before departure, and roentgenograms of the chest were made in individual cases whenever indicated by symptoms.

To the factors favoring the lower admission rates overseas, there existed a counterforce. In every theater of operations, the incidence of tuberculosis in the general population was higher than in the United States. There is

reason to believe that this higher exposure was a significant factor before the end of the war. Of men retained at separation centers in the late months of 1945 and the first half of 1946 because of X-ray evidence of tuberculosis, a significantly large majority had seen foreign service. This correlation is indicated graphically in chart 19 and is in marked contrast to the rates recorded for troops overseas and in the United States while at their respective stations. Until exhaustive research determines the origin of the lesions

CHART 19.—*Withdrawals from separation processing for pulmonary tuberculosis*[1] *in U.S. Army separation centers, July 1945 to August 1946*

[Rate expressed as number of withdrawals per 1,000 processed]



[1] Some cases withdrawn for suspected pulmonary tuberculosis, not later confirmed by further examination, are included. Not included are cases withdrawn as "other defects of lungs and pleura" and later found to be pulmonary tuberculosis.

concerned, consideration will have to be given to two possibilities: (1) The higher rate of apparent tuberculosis in men on their return from foreign duty was the result of late development of lesions acquired during Army service overseas, and (2) the relatively low rate during foreign service was due to a less effective case-finding program overseas, leaving many cases for discovery at separation centers. The latter explanation would seem not implausible, in view of the superior facilities and more stable conditions in the United States. As with other complex problems, it is probable that each of the factors named was in part responsible for the observed discrepancy.[13]

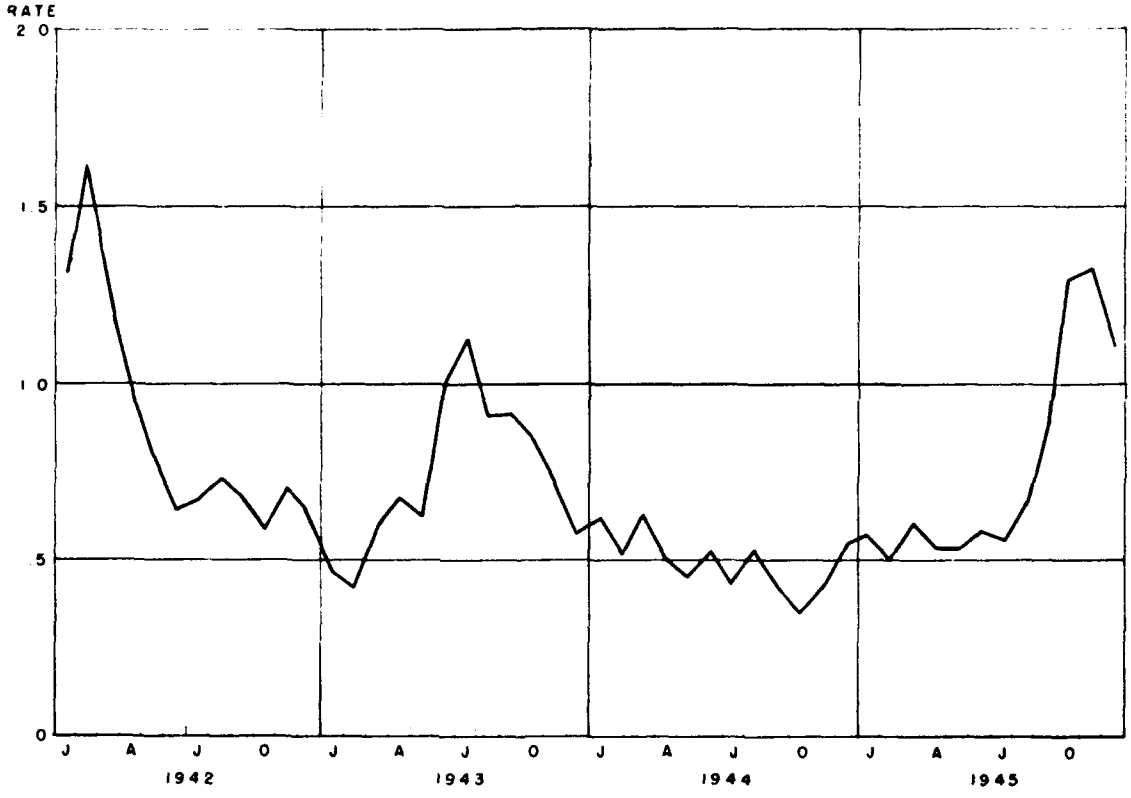
[13] Long, E. R., and Hamilton, E. L.: A Review of Induction and Discharge Examinations for Tuberculosis in the Army. Am. J. Pub. Health 37: 412-420, April 1947.

Discharges from service.—With minor fluctuations, the discharge rate for tuberculosis ran parallel to the admission rate throughout the war, averaging approximately two-thirds of the latter (chart 20). The other one-third comprised patients hospitalized for care and study, whose tuberculosis proved not to be active.

Physical standards governing discharge from service by reason of tuberculosis are discussed in another volume of the history of the Medical Department in World War II.[14] The genera as discharge of all

CHART 20.—*Disability discharges for tuberculosis among enlisted men in the U.S. Army, 1942–45*

[Rate expressed as number of discharges per annum per 1,000 troops]



men with active tuberculosis, with the exception of officers when there was reasonable likelihood that the disease could be thoroughly arrested under treatment and the officer assigned to duty of a type for which he was fitted by training and capacity. As a rule, discharge was not granted for inactive tuberculosis. Exception was made for lesions of proved activity within the period of military service and for lesions of such extent that breakdown was considered likely even though no signs or symptoms of activity were detected within the period of medical observation in the Army.

Of the several fluctuations in the rate of discharge, the only one of significance, in relation to the general admission rate for tuberculosis, oc-

14 See footnote 3, p. 331.

curred in 1943. At that time, a change in administrative policy (War Department Circular No. 161, 14 July 1943) brought about a sudden mass discharge for disability of a large number of men classified as limited service. These men did not meet current mental and physical standards for induction although at some previous period they had passed a preinduction physical examination. Tuberculosis was not an official cause for limited service in enlisted men, but it is believed that a good many borderline cases that had constituted a problem as to disposition were discharged from service during the operation of this circular, which "brought about some relaxation in the general policy of granting CDD's [certificates of disability for discharge] during that period." [15] This policy was modified (War Department Circular No. 293, 11 November 1943) by prohibiting the discharge for physical reasons of enlisted men who, although incapable of serving in a physically exacting position, might render useful service in a less exacting one.

The total number of enlisted personnel discharged from the Army for tuberculosis in the years 1942–45 was 15,387. These were divided as follows:

Year	*Number*
1942	2,400
1943	4,643
1944	3,533
1945	4,811
Total	15,387

The disease, as previously noted (p. 332), accounted for an average of 1.9 percent of all discharges for disability from disease, and was in 13th position in the listing of causes of disability discharge, the rate being exceeded, in numerical order, by psychoneurosis, musculoskeletal defects, psychosis, gastric and duodenal ulcers, respiratory diseases, arthritis, defects of the feet, neurological disease, ear disease, eye disease, organic cardiovascular disease, and genitourinary diseases.

Enlisted personnel discharged from the Army because of tuberculosis were transferred to the Veterans' Administration for further treatment if still in need of medical care, or to their own care if no longer in need of medical therapy.

Part II. Occurrence in Oversea Areas

EUROPEAN THEATER OF OPERATIONS

Incidence rates.—The incidence rate of tuberculosis in troops in the European Theater of Operations, U.S. Army, for the years 1942 to 1945, inclusive, was less than in troops in the continental United States, as a result of factors that have been described for the Army as a whole (p. 336).

[15] See footnote 7, p. 332.

Some men had entered the Army with undiscovered lesions, but many of these were detected before assignment overseas. Subsequent study, however, indicated that the relatively low rate in oversea theaters could not be ascribed solely to the exclusion of cases discovered during basic training, during special training, or incidentally to other illness. The rate of discovery at separation centers in 1945 and 1946 in troops with foreign service was significantly higher than in those who had served only in the continental United States. It does not appear that this discrepancy was due entirely to new infections acquired overseas, but, as has been noted, there is reason to believe that case-finding procedures were more effective in medical installations in the Zone of Interior, which were relatively stable in location and personnel, than in installations subject to all the vicissitudes of conflict.[16]

Lt. Col. (later Col.) Theodore L. Badger, MC, Senior Consultant in Tuberculosis, European theater, reported a relatively low rate for all forms of tuberculosis in the theater, compared with that in the Zone of Interior.[17] Incidence rates for troops in the European theater during 1942–45 and corresponding rates for troops in the continental United States are presented in table 47 for comparison.

TABLE 47.—*Incidence rates for tuberculosis in the Army in the European theater of operations and in the continental United States, 1942–45*

[Data based on sample tabulations of individual medical records]
[Rate expressed as number of cases per annum per 1,000 average strength]

Area	Year of admission			
	1942	1943	1944	1945
Europe	0. 70	0. 77	0. 85	1. 03
Continental United States	1. 86	1. 27	. 97	2. 13

The admission rate to a considerable extent reflects hospitalization of men reporting symptoms at sick call. X-ray surveys of unselected groups of supposedly healthy men, as a rule, reveal lesions in an early form that might not be expected to show symptoms for months. Such surveys were carried out under Colonel Badger's direction in England in 1943, on a total of 7,243 men. Seven cases of active tuberculosis were found, or 0.97 per 1,000 men examined. Ninety-one cases were discovered with small scarred lesions that appeared to be of no clinical significance; it may be assumed that a large proportion of them were within the group of healed lesions specified in Mobilization Regulations No. 1–9, 31 August 1940, as acceptable after a period of deferment and subsequent revaluation.

16 See footnote 10, p. 332.

17 Semiannual Report, Senior Consultant in Tuberculosis, Office of the Chief Surgeon, Headquarters, European Theater of Operations, U.S. Army, 1 Jan. 1945 to 30 June 1945.

Another survey, reported in 1945, is of interest for comparison.[18] Chest roentgenograms of officer candidates at the Army Ground Forces Officers' Training Center, near Fontainebleau, France, carried out in April 1945 by Mobile X-ray Team No. 3 of the 1st Auxiliary Surgical Group under the direction of 1st Lt. (later Capt.) Harry W. Burnett, Jr., MC, brought to light only 2 cases of active tuberculosis and 2 cases of healed infiltrative tuberculosis among 5,240 men examined. This yielded the low rate of 0.38 per 1,000 men each for active and healed tuberculosis, and a combined rate of 0.76. This group cannot be considered as fully representative of the enlisted men in the theater, for it was made up of selected men who had been sent to the officers' candidate school after field demonstration of superior mental and physical fitness.

Another survey on a selected group was that made by the 365th Station Hospital. In a report covering 2 years, from April 1942 to May 1944, while this hospital was stationed in Iceland, the section for respiratory disease made chest roentgenograms of 2,897 men from detachments of troops en route to the European theater from the United States. The commonest disease in these men was atypical pneumonia. Among the total number examined, however, there were 38 cases of infiltrative active tuberculosis and 10 cases of pleurisy with effusion of presumed tuberculous etiology. In passing, it may be noted that this relative proportion of cases of pleurisy with effusion to infiltrative tuberculosis was observed generally throughout the Army. The high proporion of active tuberculosis, namely, 1.7 percent, is not surprising in a group admitted to a hospital on the basis of respiratory symptoms. In the course of the survey, 24 cases of healed infiltrative tuberculosis were seen, yielding a rate not greatly different from that reported for the theater by the Senior Consultant in Tuberculosis.

Disposition of tuberculous patients.—The disposition of personnel discovered to have tuberculosis was based on the extent and severity of the lesion. An administrative memorandum, of 22 February 1944,[19] directed that all patients with active pulmonary tuberculosis or with large inactive fibroid lesions the stability of which was open to question, that all patients with serofibrinous pleuritis of known or suspected tuberculosis etiology, and that all patients with nonpulmonary tuberculosis should be "boarded" to the Zone of Interior.

Personnel with residual calcifications of healed primary tuberculosis or small fibrocalcific scars of infiltrative tuberculosis, apparently inactive, were returned to duty. Provision for limited duty and observation was made for borderline cases. The directive listed the tests commonly made to determine activity, including laboratory study and observation by X-ray, and ordered

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18 See footnote 17, p. 340.

19 Administrative Memorandum No. 22, Office of the Chief Surgeon, European Theater of Operations, to Surgeons, All Base Sections, Commanding Officers, All U.S. Army Hospitals, 22 Feb. 1944, subject: Disposition of Tuberculosis Patients.

that "individuals presenting an undue risk of reactivation" be evacuated to the United States.

The European theater, unlike the Mediterranean Theater of Operations, U.S. Army, had no hospitals formally established as tuberculosis centers (p. 354). Patients with tuberculosis were treated in special sections of many hospitals, with established precautions to avoid exposure of hospital personnel and other patients. Circular Letter No. 100, Office of the Chief Surgeon, European theater, dated 25 July 1944, directed that "active pulmonary tuberculosis, however small the lesion, will be treated by absolute bed rest as soon as the diagnosis has been made." It was directed also that cases of serofibrinous pleurisy of presumptively tuberculosis etiology, should be treated by bed rest until at least 2 months had elapsed after return of pulse and temperature to normal. Pneumothorax was used only for emergency cases of pulmonary tuberculosis with hemorrhage and for cases of such character that safe transport to the Zone of Interior appeared dependent on the establishment of collapse prior to evacuation. Finally, it was directed that "all cases of active tuberculosis * * * including serofibrinous pleurisy, will be boarded to the Zone of Interior in Class II, as litter patients." Evacuation was by sea and by air. Air transportation was prohibited in pneumothorax cases and for certain other patients with pulmonary tuberculosis by Circular Letter No. 102, Office of the Chief Surgeon, European theater, 4 August 1944. Air transportation was authorized for patients with early tuberculosis not sufficiently advanced to disturb respiratory function.

Incidence in nurses.—Many papers have been written on the special hazards of tuberculosis to nurses, usually ascribing it to exposure to the unrecognized open case. According to most recent reports, the incidence in nurses is higher in general hospitals than in institutions for tuberculosis. The explanation usually given is that in the latter the hazard is recognized and proper precautions are taken. In general hospitals that have no special section for the care of tuberculous patients, undetected cases admitted to the wards may constitute a significant, unguarded source for spread of the disease.

The semiannual report of the senior consultant in tuberculosis in the European theater, dated 3 July 1945, called attention to an excessive and steadily rising prevalence of tuberculosis, all forms, in nurses for the 3½ years of the war. The rates, calculated from reports from the chief nurse of the theater, as given by the senior consultant, are presented in table 48.

The mean rate for the 3½ years was 3.8 times as high as the general tuberculosis admission rate for troops in the theater. The report indicated that 19 nurses developed pleurisy with effusion of presumptive tuberculous origin, and in 3 nurses other forms of active tuberculosis were found. The pleurisy with effusion accounted for about 26 percent of the total number of cases of tuberculosis, a figure holding throughout the Army.

TABLE 48.—*Prevalence of tuberculosis, all forms, in U.S. Army nurses in the European theater, 1942–45*

[Rate expressed as number of cases per annum per 1,000 average strength]

Year	Number of cases	Strength [1]	Rate
1942	0	5,832	0.00
1943	4	24,824	1.93
1944	30	133,723	2.69
1945 [2]	38	87,004	5.24

[1] Aggregate of end-of-month strengths.
[2] First 5 months only.

Colonel Badger, in analyzing the responsible factors, called attention to the carelessness in technique that develops in times of strain and stressed the failure of medical officers to maintain proper measures designed to prevent spread of the disease in hospitals. He instituted special control measures in those hospitals in which the greatest amount of open disease was encountered; namely, the Army hospitals in France that cared for large numbers of recovered Allied military personnel liberated from German prison camps by the advancing American Army in the Saar and Rhine regions.

After the close of hostilities in Europe, when it was expected that large numbers of troops would be deployed to the Orient, specific directions were issued to make routine X-ray examination of all nurses and other Medical Department personnel prior to their departure.[20] It was impracticable to survey all personnel to be redeployed, but the special hazard of tuberculosis to personnel of the Medical Department, and particularly nurses, warranted special consideration. A few weeks later, the Japanese surrendered, redeployment to the Pacific areas was stopped, and special measures for the detection of tuberculosis were discontinued.

Incidence in Army Air Forces personnel.—Except at the beginning of World War II, enlisted and commissioned personnel in the Army Air Forces were accepted for enlisted services or appointment as officers in the same manner as Army Ground Forces and Army Service Forces troops; that is, through regular induction stations, stations for enlistment, and stations qualified to give final-type physical examinations. In the early months of the war, the demand for air force personnel was so great that aviation cadets and others were frequently accepted on the basis of a physical examination that did not include roentgenograms of the chest, with the proviso that X-ray examination was to be made at the first duty station where it was practicable. The delayed X-ray examination was effective in discovering

[20] Circular Letter No. 60, Office of the Theater Chief Surgeon, Headquarters, Theater Service Forces, European Theater, 2 Aug. 1945.

cases but had the disadvantage, from the point of view of governmental obligation, that the men discovered were in the Army and usually eligible for compensation. Later, this unusually rapid processing was discontinued, and prospective troops for the air forces were examined like selective service registrants in general.

Careful followup studies indicated a low incidence of tuberculosis after months or years of service in the Army Air Forces. A representative survey on 77,016 troops of the U.S. Army Air Forces made in England, in September 1945, with the aid of two mobile trailer 35 mm. photoroentgen units, brought to light only 70 cases of tuberculosis considered active (5 of primary and 65 of reinfection type), or 1 person in every 1,100 examined. Of the 65 cases of reinfection type, 4 were far advanced, 10 moderately advanced, and 51 minimal.[21] The group, which was almost exclusively male, and composed of 14 percent flying and 86 percent nonflying personnel, was carefully examined to determine if there was any relation between development of disease and length and type of service. The evidence of the disease discovered in flying personnel was significantly lower than in nonflying personnel, a fact attributed to the more meticulous and often repeated physical and roentgenographic examination of the former. The incidence was greater than average in men who had not had an X-ray film on entrance, or had served a longer than average period of time without a second or later film. These findings are as might be expected in view of the usual slow and insidious development of tuberculosis.

A study showed that a greater number of men who had consumed raw milk in England were among the troops with active disease than in those without disease, but the finding was believed related to the length of service rather than merely to the ingestion of the milk. The earlier a soldier arrived, the longer he stayed, and the better acquainted he became with the civilian population, the more likely he was to consume raw milk. Vigorous efforts were made by all those responsible for the health of troops to prevent consumption of raw milk in the British Isles, in view of its frequent contamination with tubercle bacilli. It was not served in army messes nor, after an initial laxity, in Red Cross canteens (p. 368).

On the whole, the Army Air Forces exhibited a gratifyingly low incidence of tuberculosis and, at the same time, disproved the view occasionally expressed that flying service predisposes to the development of active disease.

Incidence in recovered American prisoners of war.—When large numbers of American soldiers were recovered from German prison camps in the spring of 1945, it was no great surprise to medical officers to find an incidence of tuberculosis apparently surpassing the average incidence in the Army as a whole. Unfortunately, no reliable figures for tuberculosis in the thousands of recovered prisoners are available. War Department orders

[21] Wayburn, E.: Mass Miniature Radiography. A Survey in the United States Army Air Forces. Am. Rev. Tuberc. 54: 527-540, December 1946.

to make roentgenograms of all recovered prisoners before their return to the United States were in effect at the time, but an acute shortage of X-ray film and stringent measures to conserve it nullified the effect of the orders. Figures for the large group processed at Lucky Strike Camp and other camps near Le Havre are available only for those who were hospitalized. Even though hospitalization was not for respiratory disease alone it is fair to assume that a higher rate would be found than in a population not in obvious need of hospitalization. The majority of recovered prisoners who were hospitalized suffered from severe malnutrition. A number had infectious hepatitis, and acute respiratory disease was common.

In his semiannual report of 3 July 1945, the senior consultant in tuberculosis in the theater reported the incidence of tuberculosis in 2,750 recovered American prisoners hospitalized at the 77th Field Hospital, Lucky Strike Camp, as follows:

	Number of cases	*Rate per 1,000 per year*
Minimal tuberculosis	6	2.2
Advanced tuberculosis	6	2.2
Pleural effusion	9	3.3
Total	21	7.6

The rate found for all forms of active tuberculosis was thus several times the rate of approximately 1 case per 1,000 men prevailing in the Army as a whole. It is interesting to note that the incidence of pleural effusion, namely, 43 percent of the total, was higher than the usual average of 20 to 25 percent observed in hospitalized troops in the European theater and in the continental United States.

In the lack of exact studies on recovered prisoners, analysis of the reason for higher rates is speculative. Colonel Badger stressed as predisposing factors malnutrition and exposure to an environment with greater potentiality for spread of tubercle bacilli. Malnutrition is believed to be a factor in the reactivation of small arrested lesions, which, as noted in various surveys, were present in approximately 1 percent of troops. Excessive exposure to tuberculosis, if it occurred, was not direct. Recovered American military personnel were not quartered with other nationals, except in some instances where they shared barracks with British prisoners, but frequently, in the migration from camp to camp, as the senior consultant in tuberculosis pointed out in his report, they lived in dirty quarters, grossly contaminated by previous occupants, many of whom may have had tuberculosis.

At the time of writing, no significant new facts had emerged from followup studies in the United States.[22] Former prisoners of war were reproc-

[22] The study made by Long and Jablon disclosed that a significant excess of tuberculosis over the incidence for the Army as a whole occurred in recovered prisoners of war. The risk for white prisoners, chiefly captives of the Germans in this study, was three and a half times as great as for

essed at Army Ground and Army Service Forces Redistribution Centers, and X-ray examination was usually included in the routine physical examination. The largest single survey reported to the Office of the Surgeon General was from the Army Ground Forces Redistribution Station in Asheville, N.C. Ten cases diagnosed as tuberculosis were found in 1,939 prisoners of war, a rate of approximately 5 per 1,000. All of the men concerned were hospitalized and not all cases were of proved activity, so that the rate of active tuberculosis was lower. On the other hand, it must be recognized that the group examined by X-ray was to some extent an already screened group, from which men obviously ill had been removed.

In summary, it appears reasonable to conclude from the evidence that the incidence of tuberculosis did rise in men who had been prisoners of war in the European theater, to as much as five to seven times the rate prevalent in the rest of the Army (p. 391).

Incidence in recovered Allied military personnel.—In a directive from the Office of the Chief Surgeon, European theater, to the surgeons of bases, sections, and advanced sections, attention was called to the high incidence of tuberculosis in prisoners of Allied Nations recovered when the U.S. armies liberated them from prison and concentration camps in Western Germany, and to the implications for the medical and nursing personnel of the Army. Later, an order,[23] based on the sudden startling experience of Army units in the forward areas, directed a chest survey of recovered Allied military personnel, and displaced civilians, as follows:

1. Pulmonary tuberculosis of a virulent order has proved a serious problem among displaced civilians of all nationalities. The magnitude of this problem cannot be estimated at this time. It is probable that Recovered Allied Military Personnel will show an incidence of tuberculosis well above the experience of the Theater. It is imperative to establish the gravity of the situation.

2. All displaced civilians and Recovered Allied Military Personnel admitted to hospitals of the United States Army will be carefully surveyed with this thought in mind. History, physical examination, appropriate laboratory studies, and, when indicated, x-ray of the chest, will be made on all such subjects, insofar as facilities permit. Due to film shortage, x-rays will not be taken routinely.

In recovered prisoners of war of Allied Nations, U.S. medical officers found, for a time, the principal problem in tuberculosis confronting them in the European theater. At one time, the 46th General Hospital at Besançon, France, with more than 1,000 tuberculous patients of foreign nationality, was the largest tuberculosis center under control of the U.S. Army, exceeding

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men with service overseas who were not taken prisoner (Long, Esmond R., and Jablon, Seymour: Tuberculosis in the Army of the United States in World War II. An Epidemiological Study With an Evaluation of X-ray Screening. Washington: U.S. Government Printing Office, 1955).

In a special study of disease among recovered prisoners of war, Cohen and Cooper found a high rate of tuberculosis among former prisoners of the Japanese, which did not take into account the many soldiers believed to have died of tuberculosis in Japanese prison camps (Cohen, Bernard M., and Cooper, Maurice Z.: A Follow-up Study of World War II Prisoners of War. Washington: U.S. Government Printing Office, 1954).

[23] Circular Letter No. 41, Office of the Chief Surgeon, Headquarters, European Theater of Operations, U.S. Army, 11 May 1945.

Fitzsimons General Hospital, the specialty center in Denver, Colo., in its census of tuberculous patients.

Colonel Badger's report on tuberculosis in recovered Allied military personnel is quoted substantially as follows: [24]

a. *Nature of the problem*

On 18 December 1944, 304 patients of varied nationality, though mostly Russian, were admitted to the 50th General Hospital, Commercy, France. All were tuberculous. Four were dead on arrival. Ninety percent had moderate to advanced disease. Twenty-eight died of tuberculosis in the first week in the hospital, and up to 21 May 1945, 5 months after admission, a total of 101, or 33 percent, had died. Signs and symptoms of serious nutritional and vitamin deficiencies were the principal associated complications of tuberculosis or malnutrition. In the middle of March 1945, some 1,600 military and civilian nationals were sent to the 46th General Hospital in Besançon near Dijon. There were among them Russians, Yugoslavs, French, Italians, Poles, Turks, Belgians, Dutch, Czechs, Greeks, Hungarians, and Serbs. Seventy-five percent of them were Russians. A little less than half had tuberculosis, most of which, once again, was advanced disease, complicated by very severe malnutrition. Other pockets of displaced tuberculous nationals, under Third U.S. Army care in Germany, were some 7,000 men at Mauthausen, 5,000 at Nuremberg, 3,500 at Ebensee, and 3,000 at Klam. This is a glimpse of the end result of the effects of war on Allied national prisoners, both political and military.

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c. *History*

The story these men told was much the same from wherever they came. They were prisoners for an average of 34 months in the Stalag camps of Western Germany. They were for the most part captured in 1941 in the Black Sea area and the Ukraine. They were shifted from camp to camp, finally winding up in the mines and heavy industries near Metz and Sarreguemines, France, and the Ruhr region in Germany. Men were worked 12 hours or more a day with 1 day off a month, when the coal quota was filled. Maltreatment for failure to do a full day's quota of work was common. Housing was for the most part in wooden barracks of 40 to 100 feet in size, crowding in 100 to 150 men. Diets varied in different camps, but from their history and starvation state, it was apparently seriously deficient. Hygienic conditions were bad, recreational facilities were prohibited, sleeping and living conditions were congested, and hospital treatment for illness was apparently reserved for those with high fevers combined with a good prognosis. The sick were left to die in their bunks beside the living. Before capture, these men were recorded as being in excellent physical condition. Supposedly, admission to the Russian Army was by complete physical examination with an X-ray of the chest; but, if the latter was accomplished in the Russian Army, it was a monumental task. Furthermore, if only those with negative X-rays were admitted to the Army, the influence of starvation upon unseen tuberculous infection is the more striking.

d. *Clinical picture*

The typical picture of tuberculosis as seen in these patients was that of acute fulminating, rapidly fatal disease, mixed with chronic, slowly progressive, fibrotic tuberculosis. They were acutely ill with emaciation which was the combination of tuberculosis and starvation. The clinical course of approximately 30 percent was rapidly and progressively downhill. Extensive bilateral pulmonary disease was complicated by gastrointestinal, laryngeal, and bronchial involvement. Fever was varied. Many patients showed progressive, moderate to far-advanced disease in the presence of a normal temperature, some elevation of pulse, and reasonably good general appearance. The physi-

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[24] See footnote 17, p. 340.

cal findings were characteristic in the variety of signs, but the most conspicuous single feature was the presence of widespread disease with few or no physical signs. Cough and expectoration produced sputa which were heavily loaded with tubercle bacilli. Examination of direct smears showed larger numbers of tubercle bacilli than we are accustomed to see in the routine examination of sputa in the United States.

e. *Pathology*

(1) At post mortem examination, the tuberculosis was always bilateral with wide hematogenous dissemination to a variety of organs with extensive cavitation of the lungs. There was revealed more than the usual lymph gland involvement with massive enlargement of glands in both the chest and abdomen. Not uncommonly, pleural adhesions were multiple and usually obliterative, giving evidence of chronicity of the disease. Miliary tuberculosis was conspicuous by its rarity, though sporadic hematogenous spread was common.

(2) Microscopically, the lesions were characteristically fibrocaseous tubercle formation with evidence of normal tissue response to the presence of the tubercle bacilli. However, many cases presented a microscopic appearance of widespread confluent necrosis, without tubercle formation and with very little tissue reaction about the periphery of the lesion and little or no epithelioid cell formation and complete absence of giant cells. Lymphatic tissue often presented complete destruction of all lymphoid cells with tissue necrosis and often very little cellular reaction in tubercle formation.

f. *Etiology*

Etiological factors which produced this fulminating disease were undoubtedly the unusual opportunities for intense and frequent recurrent contact with seriously ill, open cases. Conditions at the German Stalag camps and at Buchenwald were such that at the latter, 46,000 people were housed in a unit originally constructed for 15,000. Sanitary conditions did not exist and where three to five men were in one small bunk and the ill were left to die unattended beside the living, the opportunities for cross infection with tuberculosis were such as have probably rarely been observed before. Everything favored the development and spread of the disease. The starvation diet with the serious degree of malnutrition undoubtedly contributed to the rapid progress of the disease. The pathology in many cases was indicative of an absence of the individual's resistance to infection.

g. *Treatment*

(1) These patients had treatment, first directed toward relief of starvation and the establishment of discipline. Language difficulties and years of living under the conditions which existed in larger work camps and Stalags made it difficult to establish any hygienic principles, or the segregation of open from closed cases. The dietary problems were not difficult to handle and those patients who were not dying of their disease improved clinically, rapidly overcoming the malnutrition per se.

(2) The *initial problem* was that of reexamining by X-ray entire groups for proper identification, diagnosis, evaluation, and therapy. Sputum-positive cases were eventually segregated from sputum-negative cases and an attempt was made to establish absolute bed rest. However, the latter proved to be practically impossible. The concept of bed rest was foreign to these men under any circumstances, and, with the Russians, it was against their principles of treatment of tuberculosis, which commanded exercise and sunshine.

(3) *Collapse treatment.*—Definitive measures of collapse were not instituted in the early weeks of treatment, except in those cases where hemorrhage indicated its necessity, or the character of the disease was unilateral and favorable to this form of treatment. It was deemed wise for these men to have 4 to 8 weeks of bed rest before pneumothorax was started, as the acuteness of the disease and the frequent presence of tracheobronchitis were not suitable for collapse therapy. Adjustment of their nutritional

deficiencies was immediately of greater concern than the tuberculosis itself. In acute widespread, bilateral disease, pneumothorax has not proved to be beneficial. Collapse therapy was never undertaken simply for the sake of "doing something" for the patient.

(4) Seen a month after the institution of treatment, those men who had not died of acute tuberculosis showed marked improvement. Order had emerged from initial chaos and reasonably good discipline had been established through the assistance of a Russian officer and aidman. It was still quite impossible to establish a regimen of absolute bed rest.

h. *Prevention*

Precautions against spread of tuberculosis were instituted first of all for the protection of U.S. Army hospital personnel and second toward segregation of the open and closed cases.

(1) Isolation technique was carried out in all the tuberculosis wards. All staff personnel wore masks and gowns. Patients wore masks when examined or treated and were taught to conceal their cough, to expectorate into small pledgets of paper which were deposited into paper bags to be burned.

(2) Floors were treated with spindle oil obtained from the British, which was applied according to directions extracted from a report prepared by the Eighth Air Force.

(3) "Clean rooms," as islands of sterility, were meticulously observed adjacent to tuberculosis wards for the protection of nurses and other personnel. No contaminated person, X-rays, records, or objects of any sort were permitted in these sanctums of cleanliness. No gowns or masks were worn or removed in these rooms. Scrub-up solutions and contaminated clothing were maintained in an adjacent room.

(4) By these means every effort was made to cut down airborne infection to a minimum and reduce the opportunity of contact to a minimum.

On 10 May 1945, Colonel Badger, Senior Consultant in Tuberculosis in the European theater, and Col. Esmond R. Long, MC, Chief Consultant in Tuberculosis, Office of the Surgeon General, conferred with Col. B. A. Osipov, member of the Military Mission of the U.S.S.R. in Great Britain and Russian liaison medical officer in the theater, with regard to the care and treatment of Russians with tuberculosis. Points of difference in treatment in the two countries were recognized, and shortly thereafter, it was decided in the Office of the Chief Surgeon, European theater, to repatriate those Russians who were physically able to travel, as rapidly as was consonant with their safety. The 46th General Hospital was made a collecting hospital for this purpose. It received recovered Russian prisoners previously hospitalized in many hospitals in France and England and effected suitable preparations for the long journey back to Russia.

Incidence in concentration camps.—In the final weeks of the war in Germany, Allied troops overran a large number of the notorious concentration camps in which the German government imprisoned political nonconformists, Jews, nationals of surrounding states, and others who had offended the Nazi Party. These camps included Buchenwald, Nordhausen, Dachau, Belsen, and many others. Thousands of dead were found in the camps at the time of their liberation, and many more thousands of sick and dying. Among the latter were hundreds of persons with advanced tuberculosis, who constituted an immediate problem for the evacuation hospitals of the advancing armies. U.S. Army hospitals rapidly developed machinery for re-

moving discovered cases from camps and placing them under definitive care. Barracks outside the camp were usually used, and in these the tuberculous were bathed, deloused, examined by X-ray, and put on immediate bed rest. In the transfer from camp, they were ably assisted by doctors of the concentration camp; that is, doctors who had themselves been inmates and had maintained primitive hospitals for tuberculous patients in the camp. Subsequently, these patients were transferred to German hospitals in the region, against the time when they could be transferred again to their own countries, or to sanatoriums in Germany. The crowding, the lack of sanitary provisions, the malnutrition and the general medical neglect, all favored progression of the disease in concentration camps. Although few figures are available, it was believed by Medical Corps officers that much of the high mortality in these camps was due to tuberculosis.

A vivid description of conditions at the Dachau concentration camp, and the extent of tuberculosis in hospitalized inmates of that camp, has been given by Piatt.[25] He made a statistical analysis of 2,267 roentgenograms of the chest of patients removed from the concentration camp hospital and examined by X-ray on admission to the receiving and evacuation section of the 127th Evacuation Hospital. In only 45.3 percent of the films was no abnormality discovered. Tuberculosis, pneumonia, and heart disease were the chief abnormalities. Six hundred and twenty-six definite cases of tuberculosis, or 27.6 percent of the total number examined, were detected. In more than half of these, the disease was bilateral, and in four-fifths of the cases, the process was either moderately or far advanced. In addition to definite tuberculosis there were 94 patients, or 4.1 percent of the total, with pleural effusion, probably tuberculous in origin. There were five cases of miliary tuberculosis.

Piatt, among others, expressed the view that the incidence of tuberculosis in Europe would increase appreciably in the years to come as a result of the return of numerous persons with undiagnosed active disease from concentration camps to their homes.

The following extract from the report of the Consultant in Tuberculosis, Office of the Surgeon General, dated 1 May 1945, also illustrates the task which faced evacuation hospitals when prisoners in concentration camps were liberated:[26]

1. *Assignment of task to 45th Evacuation Hospital.*—When the Buchenwald camp [near Weimar] was liberated a problem immediately apparent was the care and disposition of several hundred tuberculous patients under treatment in the camp. It was recognized that these were a source of dissemination of the disease, and from the point of view of medical care represented a long range problem. The processing and evacuation of these patients to a hospital appropriate for their continued care was assigned to the 45th Evacuation Hospital.

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25 Piatt, A. D.: A Radiographic Chest Survey of Patients From the Dachau Concentration Camp. Radiology 47: 234–238, September 1946.

26 Semiannual Report, 45th Evacuation Hospital, 1 Jan. to 30 June 1945. Appendix A, subject: Processing of Tuberculosis Patients From Buchenwald Concentration Camp by 45th Evacuation Hospital.

2. *Background of tuberculosis problem at Buchenwald.*—a. The conditions under which prisoners lived at Buchenwald were conducive in every way to the development and spread of tuberculosis. The malnutrition, from which every inmate suffered, together with heavy labor and harsh treatment, inevitably led to the progression of tuberculous lesions in men previously infected, whether these were originally of serious or minor character, and the intense crowding and lack of any sanitary precautions led to dissemination of infection throughout the barracks. "Block physicians," themselves prisoners, appointed by the prison administration, constantly discovered cases and sent them to hospitals established within the camp, since distinguished as the "old," the "little," and the "great." The "old" hospital, an indescribably crowded and filthy place, in which patients lay on dirty shelves in a long series of tripledecked compartments, five feet long and two feet high, six patients to a compartment, was in no remote sense a place for treatment, and in effect simply a breeding ground for the disease. In the others, thanks to the interest and intelligence of prisoner doctors, standard treatment was carried out insofar as it was possible under the desperate circumstances prevailing, with little food available, and that of the worst quality, and no relief in sight. In all of these hospitals the mortality from tuberculosis was tremendous. No accurate estimate can be made, but it is probable that many thousands of the 50,000 known to have died in the camp succumbed to tuberculosis.

b. Following the liberation a medical organization was promptly put into effect by Dr. Horn, an eminent Czech surgeon, who had been a hostage in the camp, arrested originally as a supporter of Dr. Benes. Dr. Horn was at the camp 6 years. His distinguished position was recognized by the Germans, and after November 1943 he did a large proportion of all the operative work. His capacity was universally recognized by the physicians of various national groups in the camp. Under Dr. Horn the following physicians were appointed as tuberculosis consultants: Dr. Jozef Szmeja, a Polish tuberculosis specialist, Chief Consultant; Dr. Stanislaw Machotka, a Jugoslav, who had been superintendent of a tuberculosis sanatorium in Jugoslavia, Second Consultant; and a Russian doctor who had specialized in tuberculosis.

In addition, three physicians with experience in the treatment of tuberculosis were retained in direct charge of the "great" and "little" tuberculosis hospitals (the "old" hospital having been closed with liberation of the camp): Dr. Gerhard Arnstein, an Austrian, in charge of the treatment ward in the "great" hospital; Dr. Edmund Adams, a German political prisoner of English descent, in charge of the far advanced cases in the "great" hospital; and, Dr. [Paul] Heller, a Czech, in charge of bilateral cases not suitable for specific therapy, but not hopelessly advanced, in the "little" hospital.

c. The treatment ward of the "great" hospital, with 116 cases, almost all of them under pneumothorax treatment by Dr. Arnstein, was a crowded, malodorous place in which patients slept in double-decker beds. Discipline was maintained, and patients received three times as much food as before the liberation, but no substantial improvement could be expected in such surroundings. Dr. Arnstein was conscientiously doing everything possible under the circumstances. The ward for advanced cases was simply a death room. There were thirty-two cases where there had been seventy a few days before. The "little" hospital, containing ninety-six patients, was a former stable, which had been improved by the patients themselves by the construction of windows. It was a highly crowded place filled with ambulant patients who used three-decker beds at night. There was a total lack of discipline in spite of Dr. Heller's best efforts. Three to four patients a week died there. The most that could be said for it was that it served for the isolation of ambulant patients with infectious sputum.

d. The three hospital groups just cited, made up of 244 patients, did not account for all the known cases of tuberculosis. The different national groups into which the prisoners were gathered immediately after liberation had retained some cases. Altogether it was believed that 100-150 tuberculous patients could be located in the various groups.

3. *Evacuation procedure.*—a. The above outline indicates what had been accomplished, thanks to the intelligent action of a few liberated physicians, in a short period preceding the assignment of the 45th Evacuation Hospital to the evacuation problem. The principal accomplishment of these physicians was discovery, isolation, and classification of patients, which enormously facilitated the procedure of evacuation. The institution of pneumothorax on the scale established was heroic, but much success in treatment, under the circumstances, was not to be expected.

b. A priority system, based on the emergency care required, the advisability of removal for early continuation of care elsewhere, and other considerations, was set up, whereby patients already in the Buchenwald camp hospitals were to be delivered to the 45th Evacuation Hospital at the rate of ten an hour during the working day, commencing on 28 April 1945. On the 29th the system was found to be functioning smoothly in spite of mechanical difficulties in the water line and concomitant cleaning of the hospital. Under the direction of the commanding officer, Colonel [Abner] Zehm, a remarkably rapid and effective job had been done in taking over a terribly dirty building, fouled by unrestrained, suddenly freed prisoners, with no hygienic standards, who had swarmed into the building on their release. Dead bodies were in the corridors and excrement all over the floors on arrival of the staff. Two days later, when evacuation operations commenced, the place was clean and normal operation was in progress.

c. A dispensary organization has been set up by Dr. Horn in Buchenwald Camp for diagnosis of new cases from suspects sent in by physicians in the barracks, which still housed some 15,000 ex-prisoners. The selection is based entirely on symptoms. In the opinion of the undersigned the number of cases would run far beyond the expected 150 cases if a more careful method of selection including X-ray examination were possible. In view of the tremendous exposure to which the group has been subjected, cases will inevitably arise in considerable number for years to come. At present only the method indicated is practical. The dispensary will hold 35 patients for observation at one time, and it is expected that by the time the present 240-250 patients have been evacuated the dispensary can conclude the remaining task in a few days.

4. *Organization of the 45th Evacuation Hospital.*—a. The staff consists of the commanding officer and 20 medical officers. Lt. Col. [Isidore A.] Feder, MC, Chief of the Medical Service, has instituted an organization which admirably combines simplicity and efficient operation. Ten 40-bed wards, each in charge of a medical officer, have been set up. In addition to these there is a receiving officer, a general internist, an X-ray chief, a laboratory chief, and a specialist in ear, nose, and throat work. The rest of the staff of 20, composed of members of the surgical team, are at present on other duties in the area.

b. On arrival at the hospital, patients are taken to the receiving wards (one for ambulant and one for litter patients) and their records are initiated by the receiving officer. By arrangement with the doctors at Buchenwald camp, their previous medical records are sent with them. EMT's [emergency medical tags] are made out, and a simple medical record devised by the 45th Evacuation Hospital, entirely suitable for the purpose, is started. After this, patients move across the hall, where their clothes are taken away from them to be destroyed, they bathe in hot showers, and are dried and sprayed with DDT [dichlorodiphenyltrichloroethane]. Then they receive clean pajamas and are sent to the X-ray room, where a roentgenogram is made of each man, with a Picker field unit, the subject holding the cassette in his arms. The pictures made are remarkably good, with all the required detail and excellent contrast. Much credit is due to the technician in the dark room, for the condition of the electrical line requires relatively long, fixed exposure and fixed kilovoltage so that careful individual processing in the development tanks is necessary. After the X-ray film is made each patient is sent to his ward. Shortly afterwards, clinical histories are taken through an interpreter, and specimens are obtained for laboratory examination—sputum, blood,

and urine being examined routinely. Blood sedimentation rates are determined in cases where tuberculosis is diagnosed but the patient is afebrile. The whole procedure is handled quietly and expeditiously.

c. Special mention should be made of the work of the enlisted men. Good technical work is done in the X-ray department and laboratory as well as the bath department, and the care given by the litter bearers, as observed by the undersigned, was superb. Very sick, suffering patients were transferred from litters to cots with infinite gentleness, which, in the light of the bestial brutality which had been the lot of the patients in Buchenwald camp prior to their liberation, was extraordinarily impressive.

5. *Assessment of the evacuation procedure.*—a. The work done by the 45th Evacuation Hospital in processing tuberculous patients is excellent. Dr. Horn, who had observed the care of tuberculous patients at Buchenwald for years, was strong in his tribute to the spirit and standards of the Medical Department of the U.S. Army. No words can describe the relief and joy of the patients. After their long misery in the filth and torture at Buchenwald, the clean sheets and blankets and personal solicitous attention of the 45th Evacuation Hospital were incredible luxuries.

b. The medical processing meets its purpose in every way. The objective of the hospital is to effect machinery for suitable transfer of patients to permanent quarters. Status as ambulant and litter patients is being established in a sound manner. A certain number of cases misdiagnosed as tuberculous are being discovered, and will be returned for such medical care as they require. Some patients will be found who are too sick to move further under any circumstances, and terminal care is being provided. Treatment is quite properly by rest and good food, which is enormously appreciated by the patients. Pneumothorax treatment is not being given and does not appear indicated in the expected short period of retention of the evacuation hospital. It is believed that refills, if necessary in any cases, can be given, by special arrangement, by the camp physicians who initiated the procedure.

Under arrangements effected by the Office of the Surgeon, Headquarters, First U.S. Army, the tuberculous patients evacuated from the Buchenwald concentration camp were transferred to a permanent German hospital at Blankenhain near Bad Berka and Weimar for continued care pending later transfer of suitable cases to their homes in liberated countries. It was recognized that a majority of the patients were too ill to recover and would remain a charge of that department of military government concerned with the hospitalization of displaced personnel (pp. 397–399).

NORTH AFRICAN AND MEDITERRANEAN THEATERS OF OPERATION

Admission rates.—As in the European theater, the recognized incidence of tuberculosis in the Army in the North African and Mediterranean theaters was lower than in the Zone of Interior. During 1942–45, approximately 1,300 cases with active or inactive tuberculosis were admitted to medical treatment facilities for observation or care, an incidence rate of 0.85 per 1,000 per year. In a study involving 800 cases, 57 percent were classified as active and 20 percent as probably active, the remainder as inactive or uncertain.[27]

[27] McKean, George T., and King, Donald S.: Survey of Tuberculosis and "Primary" Pleural Effusion for the Period of Activity of NATOUSA and MTOUSA to 1 Apr. 1945, vols. I and II. [Official record.]

In the aforementioned study, diagnosis, treatment, disposition of cases, and the epidemiology of tuberculosis in the theater were discussed at length. In addition, special attention was devoted to primary pleural effusion, which was a problem of unusual significance.

In a high proportion of cases, symptoms, principally cough, led to hospitalization; a smaller number were discovered in various types of routine survey. Laboratory facilities varied in the theater, but even in forward hospitals means for staining tubercle bacilli were available and X-ray examination could be made. Films from field and evacuation hospitals were of good diagnostic quality; in general, the diagnostic work was of superior character.

Differential diagnosis frequently involved distinction from atypical pneumonia, and occasionally from chronic pulmonary diseases other than tuberculosis. The chief difficulty in diagnosis was determination of activity. In sputum-positive cases this was no problem, but decision was difficult in the numerous cases where a small fibrotic lesion was evident in X-ray films. The usual and most important single aid, namely, a long series of films for comparison, was not available, because circumstances did not permit retention of patients for the necessary length of time. Consequently, individual judgment, based on all data available, was most important.

The annual rate of admission in terms of troop strength was approximately the same for Negro as for white soldiers. Negro soldiers constituted 9 percent of the total strength, but contributed only 7.5 percent of cases up to April 1944. On 31 March 1945, Negro troops constituted 13.5 percent of the total strength in the theater and, by that time, accounted for 15 percent of the cases of tuberculosis. Analysis by type of case indicated that the disease was of distinctly greater average severity in Negro than in white soldiers. In the former, there were more bilateral cases, more cases with cavity, more of exudative character, and a lower proportion of cases considered inactive. According to data obtained from individual medical records, there were 60 deaths during 1942–45 among U.S. Army personnel admitted for tuberculosis in the Mediterranean theater. Many patients who were evacuated died elsewhere. Of the 60 deaths, 50 were among male enlisted personnel; 30 of the 50 deaths were among Negroes.

Hospitalization.—In the North African and Mediterranean theaters, as in all theaters, tuberculous patients were initially admitted to hospitals of all types. Admissions were about equally divided among soldiers from the Fifth U.S. Army, the Army Air Forces, and Army Service Forces. Unlike the other theaters, the North African and Mediterranean theaters established tuberculosis centers for the reception of cases from other hospitals and for study with a view to appropriate disposition. The following hospitals served this purpose: 6th General Hospital, Casablanca, French Morocco; 24th General Hospital, Bizerte, Tunisia; 17th General Hospital, Naples, Italy, and the 64th General Hospital, Leghorn, Italy. The concentration of medical officers, with special training in a few centers equipped for definitive treatment, in-

sured an adequate number of beds and a high type of professional care for patients prior to their evacuation to the United States. These hospitals were frequently visited by Lt. Col. (later Col.) Donald S. King, MC, Chief, Medical Service, 6th General Hospital.

Analysis of data for a representative group showed that the average duration of hospitalization of active cases, prior to evacuation to the Zone of Interior, was 58.5 days. From this figure, based on a large sample, it was calculated that active cases of tuberculosis were responsible for 22,405 days of hospitalization in the theater. Only 24 patients, however, remained in a theater hospital more than 3 months.

Also admitted to Army hospitals in this theater were tuberculous patients from the armies of our Brazilian and British allies, tuberculous prisoners of war, and occasional patients in other categories.

Therapy and disposition.—Hospital care being, as a rule, of relatively short duration in the theater, definitive treatment was not so intensive as in tuberculosis centers in the United States. However, in many cases, temporizing was contraindicated; collapse measures were instituted promptly to prevent serious progression, although this practice anticipated the type of care to be given during prolonged hospitalization in the United States and the pneumothorax had to be maintained during evacuation to the Zone of Interior, at ports of debarkation, and en route from the latter to tuberculosis centers in the United States.

The indications for pneumothorax were the usual ones; namely, unilateral excavation, spreading infiltration, and persistent hemoptysis. The following policy was drawn up in the late months of the war with respect to collapse therapy and the type of transportation most appropriate for different categories for evacuation to the United States.[28]

1. Pneumothorax treatment in the theater should be limited to predominantly unilateral cases, with evidence of cavity formation or rapid extension, for which transportation to the United States is not immediately available, and such cases should be evacuated on hospital ships equipped to continue pneumothorax after this treatment has been established.

2. Bilateral advanced cases and advanced cases for other reasons unsuitable for pneumothorax should be treated by continued rest and returned to the United States by hospital ship as soon as space is available.

3. Unilateral and bilateral cases of active disease of minimal extent, without gross evidence of cavitation, should be sent to the United States by air at the earliest possible moment, and treatment, other than rest and hygiene, in such cases should not be attempted in the theater.

4. Cases of pleural effusion without other demonstrable etiology should be considered as probably tuberculous and evacuated to the United States by hospital ship, after termination of the acute phase of the illness, for treatment and disposition.

5. Under ordinary circumstances moribund cases should not be evacuated to the United States.

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[28] Memorandum, Col. Esmond R. Long, MC, Consultant in Tuberculosis, to The Surgeon General, U.S. Army, 18 Apr. 1945, subject: Visit by Consultant in Tuberculosis, Office of the Surgeon General, in Mediterranean Theater of Operations.

6. Individual judgment should be exercised in the case of small, scarred and probably inactive lesions, with evacuation to the Zone of Interior in those cases where the lesion in question is of truly doubtful stability, opportunity for continued observation of the case is unlikely and key personnel are not involved.

Pleurisy with effusion.—Pleurisy with effusion, presumptively tuberculous, was frequent in proportion to the total number of cases of tuberculosis. In 1944, there was an apparent increase during the summer months, the reason for which never became clear. It was considered possible that numerous infections might have occurred in crowded quarters during the winter, becoming manifest several months later in the form of effusion.

In 16 out of 33 carefully studied cases, the bacteriological diagnosis determined by guinea pig inoculation, culture, or other means, was positive for tubercle bacilli. A diagnostic problem was distinction from the effusion that sometimes accompanies atypical pneumonia. In general, however, it was believed that large effusions were rare with this type of pneumonia, whereas the effusion of tuberculosis was frequently massive.

Altogether, 265 cases of primary pleural effusion were encountered, of which 229 were evacuated to the Zone of Interior. Two were reclassified to limited service and 30 were returned to duty. The wisdom of the latter course was later seriously questioned, in view of the frequency with which late tuberculous parenchymal infiltration follows pleurisy with effusion. Three-fifths of the cases were in soldiers 25 years of age or less.[29]

Epidemiology.—Much attention was devoted by medical officers to the epidemiology of the disease in the North African-Mediterranean theater. Up to June 1944, the number of cases evacuated to the Zone of Interior, although not considered alarming, was recognized as significant.[30] In the summer of 1944, the centralization of patients in special hospitals brought to light the fact that not infrequently there was an abnormally high incidence of disease in individual units, and an index system was set up to aid in tracing sources of infection. New patients were questioned as to previous contacts in the Army, and from time to time, new additions to already known endemic foci were thus discovered. In one medical battalion headquarters and headquarters company, consisting of 50 enlisted men and 7 officers, 8 cases of pulmonary tuberculosis or pleural effusion were found. Contacts with Italian civilians that may have been a source of contagion were believed to occur, but could not be traced with similar accuracy.

In this connection, Circular Letter No. 41, Office of the Surgeon, Headquarters, North African Theater of Operations, dated 29 July 1944, directed the following:

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[29] A postwar study of 141 cases of primary serofibrinous pleural effusion in World War II soldiers, in which observation was continued for 5 or more years after diagnosis, disclosed a high incidence of relapse in men returned to duty following absorption of a pleural exudate. In cases where hospitalization was brief and return to duty correspondingly early relapse occurred in approximately 90 percent of persons (Roper, W. H., and Waring, J. J.: Primary Serifibrinous Pleural Effusion in Military Personnel. Am. Rev. Tubere. 71: 616 634, May 1954).

[30] Custer, E. A.: Tuberculosis in the North African Theater of Operations [and appended Comments by the Theater Surgeon]. M. Bull. North African Theat. Op. (No. 6) 1: 30 31, June 1944.

It will be the responsibility of the commanding officers of "tuberculosis reception centers" to notify the medical officer of any organization, in which an "open case" of tuberculosis is discovered, of the existence of such a case, and it will then be the responsibility of the unit medical officer to initiate promptly such studies as are considered necessary for the detection of pulmonary tuberculosis in intimate contacts of the patients.

Routine surveys, made on several units, were occasionally fruitful. In one survey made after discovery of an open case, no case of definitive active tuberculosis was found among 718 persons, including 52 officers and 123 women, but 16 lesions of minimal extent were discovered, 8 of which were considered possibly active, the remainder, probably inactive.[31]

Although Italian civilians were always suspected as a source of serious contact, adequate study was not made until after the end of hostilities. Some evidence of special danger was found by the Chief of Medical Service, 15th Evacuation Hospital in a survey of approximately 300 civilian foodhandlers in the Milan-Turin region. Of these, 15 (or 5 percent) had clinically significant tuberculosis of reinfection type.

Evacuation.—Patients were evacuated by sea and by air. In the early days of the theater, most tuberculous patients came home on troop transports. Later, the majority returned in hospital ships, when these were available in sufficient number. It was recognized that far better care could be given them on hospital ships, where special quarters could be assigned and where X-ray and pneumothorax equipment and laboratory facilities were readily available. At the same time, isolation technique protected other soldiers from exposure to contagion. Fortunately, there was little communicable disease other than tuberculosis requiring evacuation from the theater. Accordingly, it was possible, in many voyages from Italy to the United States, to use for tuberculous patients the entire section of the ship that had originally been set aside for contagious diseases. This section usually provided airy 8- and 12-bed wards.

SOUTH PACIFIC AREA

Incidence.—In reports for the years 1942–45 for the South Pacific Area (New Caledonia and the Solomon Islands), an admission rate for tuberculosis of 1.5 per 1,000 men per annum is shown, except for the year 1942, when the admission rate for the last quarter only is recorded and was 2.1. Incomplete reporting, mistakes in diagnosis, inclusion of readmissions and transfers are mentioned as factors causing inaccuracies. It was believed by the reporter, however, that the errors did not exceed 10 percent. The totals for the 4 years, as reported, were: 1942 (last 3 months), 42; 1943, 214; 1944, 264; 1945, 57. The incidence rates, taken from the statistical health report (WD MD Form 86ab) in the records in the Office of the Surgeon General, were: 1942, 1.38; 1943, 1.20; 1944 (consolidating South Pacific with Central Pacific Area to

[31] Wyman, S. M.: Report of a Roentgenologic Chest Survey. M. Bull. Mediterranean Theat. Op. 3: 15–16, January 1945.

make Pacific Ocean Area), 0.71; 1945 (also consolidated), 0.95. The average rate for the Pacific Ocean Area for 1942–45, inclusive, was 0.86.

Types of tuberculosis.—The majority admitted to hospital were cases of pulmonary tuberculosis. It is interesting to note that of 82 cases of chronic reinfection type pulmonary tuberculosis admitted, 32 were recorded as minimal, 38 as moderately advanced, and only 12 as far advanced. In a theater where examinations were usually made on the basis of symptoms rather than through the medium of mass X-ray surveys, the preponderance of minimal and moderately advanced cases indicates that medical officers were on the alert for cases and recognized the need for their discovery before the disease reached the far advanced and generally hopeless state.

Fifteen cases of tuberculosis of the genitourinary tract were positively identified out of a much larger number of cases of genitourinary tract disease in which the diagnosis was questionable. It is noteworthy that in the Central and South Pacific Areas (data for the areas separately are not available) 40 cases of tuberculosis of the genitourinary tract were found, yielding a rate of 2.8 per annum per 100,000 average strength. This may be compared with 1.8 for the Southwest Pacific (based on 28 cases) and 2.7 for the total Army (based on 674 cases). It may be noted here that, although pulmonary tuberculosis was generally excluded through X-ray examination at induction stations, facilities for detection of genitourinary tuberculosis were usually inadequate, so that cases that were asymptomatic at the time of induction were unknowingly accepted.

Of the nonpulmonary forms, tuberculosis of the pleura was conspicuous (9 cases). There were a few cases of tuberculosis of superficial lymph nodes, bones, joints, and meninges. The list included only one case of generalized miliary tuberculosis.

Diagnosis.—Diagnostic facilities varied with the type of medical installation and its location. First-class roentgenological facilities were available throughout the theater and, according to the official reports, liberal use was made of them at all times. Every patient with symptoms of chest disease was examined by X-ray. Group surveys were made when special circumstances indicated their value. For example, a Navy steward was found to have advanced pulmonary tuberculosis and about 20 close contacts were studied. It was interesting to note that no active cases were found in this study but that two or three apparently inactive cases were located.

Facilities for laboratory examinations depended upon the proximity of the installation concerned to the front. Laboratories as far forward as clearing companies had all the necessary equipment for making stains for acidfast bacilli. In installations to the rear of clearing companies, facilities were available for concentration methods for the detection of tubercle bacilli, and in such installations gastric lavage was performed. General hospitals made considerable use of cultural methods for detection of tubercle bacilli. Guinea-pig inoculation was resorted to occasionally in medical laboratories, for example,

in the 6th Medical Laboratory on Guadalcanal. In view of the scarcity of the animals, this was largely restricted to cases in which tuberculosis of the kidney was suspected.

Hospitalization and care.—Few officers who had specialized for a long period in tuberculosis were on duty in the theater, which in this respect was worse off than the European and Mediterranean theaters. Because of the great distances involved, the consultant system was not used. The diagnosis and treatment of tuberculosis thus depended upon the judgment and general medical ability of officers in the various installations.

Patients were transferred from installations where the diagnosis was made to general hospitals in the theater for observation, care, and disposition. Therapy was restricted largely to rest and measures directed toward improvement in general nutrition, supplemented by symptomatic treatment for relief of cough and pleuritic pain. Collapse therapy was seldom attempted, since it was the policy of the theater to return all cases needing definitive care as promptly as possible to the United States.

Special problems.—Medical officers were on the lookout for special effects of climate and other adverse conditions peculiar to the region.

Climatic conditions were highly variable throughout the area, which, at one time or another, extended from the equatorial latitudes of the Bismarck Archipelago to the Temperate Zone of New Zealand and from the 150th meridian of east to the 150th meridian of west longitude. The majority of the troops in the command lived under tropical and semitropical conditions in the Solomon Islands and in New Caledonia, although a certain number were stationed in New Zealand for extended periods for training or rest. No specific effects attributable to the climate were emphasized by medical officers in the area.

Service in these regions was arduous. Corresponding with the number of troops involved, the amount of tuberculosis discovered was highest in the infantry, in which more than a quarter of the cases detected were found. It is remarkable that the next highest number of cases were discovered in personnel of the Medical Department, and a slightly lower number, in the Corps of Engineers. These three branches accounted for more than half of all the cases of tuberculosis discovered. The highest rate of tuberculosis recorded in the theater was during the period of most intense combat. This, however, was a period when a large proportion of troops that had been relatively poorly screened in the United States were on duty in the theater.[32] In the opinion of the reporting official, the relatively high incidence discovered in the first 3 months of recorded data for the theater (end of 1942) was probably the result of this imperfect screening rather than the unusual severity of the service itself.

Likewise, no specific correlation with nutrition was discovered. Nutrition was in fact relatively poor at the time that the troops were most heavily

[32] See footnote 3, p. 331.

engaged in combat and the incidence of tuberculosis was at its highest. Some medical officers attempted to determine if tuberculosis decreased after improvement of the diet, which consisted largely of C and K field rations in the earliest part of the war, but no significant conclusions in this respect could be drawn. Certainly, nutrition improved enormously after the first difficult period, but it was true also that the troops chiefly concerned at this later time had been subjected to much better screening.

In view of the high prevalence of malaria and other tropical diseases, a number of medical officers attempted to determine if they had any effect in activating tuberculosis. No specific evidence of activation of tuberculosis as a result of concomitant malaria or other disease was detected. This corresponds with the results of a number of prewar studies, which failed to show any specific connection between malaria and depression of resistance to tuberculosis.

Mortality.—The number of deaths from tuberculosis in the theater was extremely small. In the theater report, only five fatal cases are listed, all of them of acute type. The death rate deduced from these figures was 1.3 per 100,000 men per annum. The figure merely indicates that cases of ultimately fatal issue were transferred to the United States before death occurred.

Evacuation.—All patients with active tuberculosis of any part of the body were evacuated to general hospitals in the United States. A total of 158 patients were evacuated from New Caledonia and 65 from Guadalcanal. In the early months of the war, a few patients were sent to Melbourne, Australia. Evacuation was ordinarily by direct transfer to a medical installation in the United States. The largest number of transfers was to Letterman General Hospital, San Francisco, Calif.

Patients with active pulmonary tuberculosis were almost invariably evacuated as strict litter patients, whether the transfer was by air or by sea. Patients with inactive or arrested tuberculosis and those with involvement of superficial lymph nodes only, as well as a good many cases of genitourinary and other forms of nonpulmonary tuberculosis, were evacuated as ambulatory patients. Evacuation by air from New Caledonia commenced in 1943 and increased notably in 1944 and 1945. However, even at the end of the war, from this distant area, the majority of patients were returned to the United States by ship. Approximately 13 percent were returned by air. Of the 158 patients returned by ship from New Caledonia, 66 percent were litter patients, 23 percent ambulatory patients, and 11 percent troop-class patients.

SOUTHWEST PACIFIC AREA

Incidence.—In comparison with other medical problems, tuberculosis was considered of minor military significance in the Southwest Pacific Area.[33] The official report from the area states:

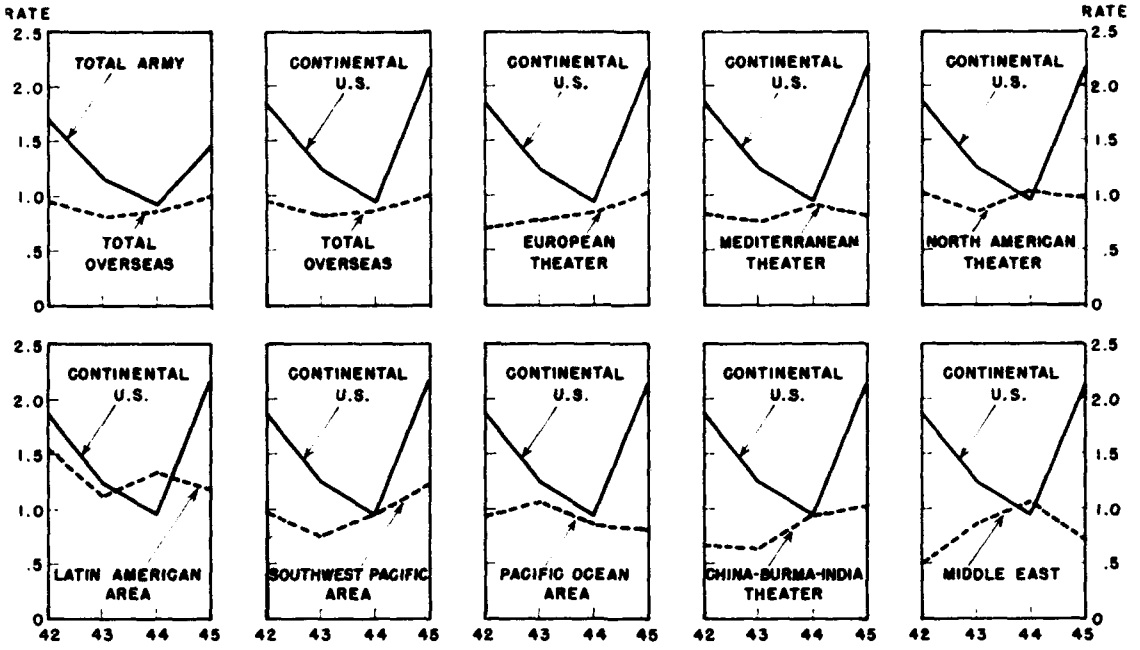
[33] Timpanelli, Alphonse E.: Tuberculosis in the Southwest Pacific Area [World War II]. [Official record.]

* * * in 40,000 continuous admissions for all causes from all sections of the Southwest Pacific area in two large general hospitals operating at various times in three seperate areas in New Guinea and the Philippines, only 64 cases of tuberculosis were found * * *. Of these 64 cases studied, 62 were instances of pulmonary tuberculosis and 2 of tuberculous cervical adenitis without clinical pulmonary involvement. Extra-pulmonary tuberculosis was rarely encountered in the area. A review of the pulmonary cases showed that 12 were diagnosed as inactive or arrested, 33 as minimal active, 16 as moderately advanced, and 1 far advanced. None of the patients were critically ill and none died in the theater.

The incidence rates for tuberculosis in the Southwest Pacific Area and other theaters and areas, as computed in the Office of the Surgeon General,

CHART 21.—*Incidence of tuberculosis in the U.S. Army, by theater and year, 1942-45*

[Preliminary data based on periodic summary health reports]
[Rate expressed as number of cases per annum per 1,000 average strength]



are shown in chart 21. The rate for all theaters and areas during World War II was 1.25.

Diagnosis and care.—Medical installations in general were provided with X-ray and laboratory facilities, so that diagnosis was ordinarily made at an early stage. Cases discovered in forward areas were evacuated to general hospitals where, in most instances, one or more members of the medical staff had had specialized training in tuberculosis. Laboratories were regularly equipped for examination of sputum and gastric washings and the determination of sedimentation rates.

Special medical problems.—As in the South Pacific, an effort was made to determine if climatic conditions or prevalent tropical diseases played a role in the activation or progress of tuberculosis. No evidence was found that these factors played any part in increasing the incidence or severity of tuber-

culosis. Comparative studies showed that prevalent bacterial infections and parasitic infestations were no more common in tuberculous patients than in the general population of patients. The official reporter records:

> While the groups of patients admitted in various periods from areas of prolonged and active combat showed, in general, varying degrees of undernutrition and physical exhaustion and a greater incidence of parasitic infestation, they presented no more tuberculosis than was seen among patients from service forces operating under more favorable conditions.

Evacuation.—Cases of active tuberculosis were evacuated as rapidly as possible after the final decision was reached by the disposition boards of the hospitals concerned. Wherever possible, tuberculous patients were transferred to the United States by air. It was felt that the best assurance possible for recovery was to minimize delay in the initiation of definitive treatment in a specialized Army medical institution in the Zone of Interior. "In the few instances in which evacuation from the theater for old, well-healed pulmonary lesions did not seem warranted, arrangements were made for periodic examination and evaluation."

In general, definitive therapy was not attempted in the theater; it was felt that the type of treatment to be employed in individual cases should be left to the installation charged with the final care of the patient. The report states further that "the short period of time which the patient spent in the oversea theater hospital was utilized in educating him in regard to the nature of his disease, in his personal care, and in isolation technique. He was kept in isolation and on bed rest during his stay in the hospital and en route to his destination."

The official report states that "air travel was well tolerated by patients in all stages of the disease. No complications incident to air travel arose in patients with tuberculous pulmonary lesions."

The average period of hospitalization between diagnosis and evacuation was 18 days.

WESTERN PACIFIC BASE COMMAND

Incidence.—The official report for this command states that about 0.6 percent of a series of approximately 18,000 medical cases were diagnosed as tuberculosis. The incidence rate in the command for the period June through September 1945, as recorded on the statistical health report, was about 1 per annum per 1,000 average strength. The great majority of the cases were of pulmonary tuberculosis. In addition, there were a few cases of genitourinary, miliary, bone, and gastrointestinal tuberculosis, and tuberculosis meningitis.

Diagnosis.—The most frequent problem encountered was in early differentiation of tuberculosis from atypical pneumonia. Repeated examination of sputum and gastric washings for tubercle bacilli in many cases resulted in a diagnosis that could not be made on the roentgenogram alone. Bronchiectasis and coccidioidomycosis also required differential diagnosis. Cases of bron-

chiectasis were not uncommonly seen, but were not accurately diagnosed, for the medical officers in the area were reluctant to use Lipiodol because of possible future confusion on reexamination at tuberculosis centers in the United States. Cultural methods were employed in isolating tubercle bacilli; guinea pigs were rarely used because of their scarcity in the theater. The standard methods were used for determination of activity of tuberculosis as bearing upon disposition.

Treatment.—As a rule, initial treatment only was attempted. The principal therapeutic problem was whether to institute pneumothorax prior to evacuation. This was rarely done, because of (1) uncertainty concerning route, mode, and speed of evacuation, (2) uncertainty whether competent personnel would be in attendance en route to give refills and handle possible complications, such as tension pneumothorax, and (3) the need for a long period of bed rest and observation prior to institution of collapse. Collapse was, however, induced in cases of persistent hemorrhage, cases in which excavation developed in rapidly progressive lesions, and cases in which there was reason to believe adhesions were forming.

Special problems.—The official report stated that "* * * no medical officer contacted had definite basis for believing that the tropical climate per se influenced the development of tuberculosis, although it was a factor in determining disposition of certain cases * * *. Nor could the type of military service be correlated with the incidence of tuberculosis. Most of the officers who dealt with repatriated prisoners of war believed that their poor nutritional status undoubtedly influenced their high rate of tuberculous infection." The subject of tuberculosis in recovered prisoners of war is treated elsewhere. It will be noted here that a survey of troops from Iwo Jima, where supplies of fresh food were probably least adequate, failed to demonstrate a clinical deficiency status that could be correlated with the progress of infectious disease of any type. Subclinical vitamin deficiencies were slight, and of no greater severity than were seen in a similar group in the Hawaiian Islands.

Evacuation.—Evacuation by air was considered the ideal form of transportation, but was not available as often as was desired. Prior to evacuation, whether by sea or by air, sedation with barbiturates was given, and provision was made for such complications as spontaneous pneumothorax. All patients with active tuberculosis were evacuated, and a good many with lesions that were without symptoms or signs and appeared to be inactive on X-ray examination were, nevertheless, evacuated to the United States because medical officers in the command did not feel justified in calling such cases arrested without prolonged observation. With the end of hostilities, as the report notes, the tendency of the theater was to be more liberal with the diagnosis of inactive tuberculosis, and, for this reason, numerous patients of types previously forwarded to the United States were held for prolonged observation, and not infrequently returned to duty.

MIDDLE PACIFIC

Incidence.—The incidence of tuberculosis in the Pacific Ocean Area, which consisted of the combined Central and South Pacific Areas, is shown in chart 21. A sampling comprised of admissions in the Middle Pacific command during the first 11 months of 1945, shows a total of 164,957 cases of disease of all types, including 287 cases of tuberculosis, or 0.17 percent of all admissions.

Diagnosis and care.—Nothing unusual in diagnosis, not seen in other parts of the Pacific area, was noted in the official report in the Middle Pacific command. Hospitals in the Hawaiian Islands were excellently equipped, so that every procedure that could be carried out in the Zone of Interior was readily available. Because of the accessibility of six excellent general hospitals, definitive care was instituted more frequently than in the more remote areas in the Pacific. Active cases were transported as soon as convenient to the mainland. As in other parts of the Pacific area, medical officers concerned with the care of tuberculous patients did not attribute any particular manifestations of the disease to climatic peculiarities of the region, to the type of service, or to the malnutrition that from time to time affected substantial numbers of troops in combat.

Evacuation.—The majority of patients with tuberculosis were transported to the Zone of Interior by water, except that those who were sent by way of the Hawaiian Islands accomplished this part of the journey by air.

CHINA-BURMA-INDIA THEATER

Tuberculosis in military personnel was not considered a serious problem in the India-Burma theater.[34] The consultant in medicine in the theater reported that 334 cases were admitted to hospitals there between the first of January 1944 and the end of July 1945. The annual incidence rates per 1,000 average strength and numbers of cases for the China-Burma-India theater, based on preliminary sample tabulations of individual medical records, are as follows:

	Number of cases	*Rate*
1942	6	0.69
1943	27	.68
1944	157	.93
1945	240	1.04

On the other hand, Army installations in the China and the India-Burma theaters recorded a high incidence of tuberculosis in Chinese troops. The great majority of tuberculous patients in U.S. Army hospitals in China and

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34 (1) Blumgart, Herrman L., and Pike, George M.: History of Internal Medicine in India-Burma Theater, p. 118. [Official record.] (2) The U.S. Forces, India-Burma Theater, was created on 24 October 1944 by dividing the U.S. Forces, China-Burma-India into two separate theaters—the China Theater and the India-Burma Theater.

Burma were Chinese. Because of this high incidence and the notorious lack of sanitary precautions observed by sick Chinese soldiers, medical and nursing personnel in these hospitals were heavily exposed to contagion. Routine checks by the 48th Evacuation Hospital of hospital personnel failed to disclose cases of tuberculosis that could be traced to contact in the theater. Since, however, tuberculosis is slow in its evolution, and years may elapse between infection and manifest disease, it was recognized by administrative officers of these hospitals that persons who had been employed in them should be carefully observed for some time after their return to the United States.

ALASKAN DEPARTMENT

From time to time, concern was expressed over the extent of tuberculosis in Alaska. Reports from units in the Alaskan service called attention to the excessive admission of men with tuberculosis through the enlistment process at Alaskan stations, where facilities for the detection of the disease were inadequate. Attention was also called to the danger of exposure of servicemen to tuberculosis in Alaska, where the prevalence of the disease greatly exceeded that in the United States. During the war, negotiations were underway for the construction of a hospital for the care of tuberculous patients in Alaska, and the danger to servicemen, through contact with nonhospitalized cases, was cited as emphasizing the need for such a hospital. The number of nonhospitalized open cases in the territory was estimated by the Office of the Surgeon General as approximately 1,000 and, although the distribution of these cases was unknown, it was assumed that their presence in communities where troops were stationed constituted a hazard in contagion.[35] In addition, the factor of exposure to harsh climatic conditions, with an adverse effect on small latent or unrecognized tuberculous lesions, was also cited as reason for special consideration of the problem of tuberculosis in the Alaskan Department.

The actual incidence rates for tuberculosis during the war years, however, did not reflect an unusual hazard. The annual rates per 1,000 men, based on preliminary summary reports, were much like those recorded elsewhere:

	Number of cases	*Rate*
1942	81	1.61
1943	99	.86
1944	70	.84
1945	44	1.07

Whether evidence of infection acquired by soldiers in Alaska will develop later, could not be predicted.

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[35] Memorandum, Lt. Col. Robert J. Carpenter, MC, Executive Officer, Office of the Surgeon General, for Assistant Chief of Staff, G–4, attention: Col. Carroll H. Deitrick, GSC, Chief, Policy Branch, 15 Mar. 1944, subject: Hospitalization for Tuberculosis Cases in Alaska.

LATIN AMERICAN AREA

As in Alaska, troops in the Caribbean area and in Central and South America served in regions of relatively high prevalence of tuberculosis in the local population. Also, as in Alaska, the troops on duty included a good many recruited locally from a territory of the United States where the prevalence of tuberculosis was high; for example, Puerto Rico. The total incidence rates, however, up to the end of the war did not furnish evidence of special hazard. The annual incidence rates per 1,000 average strength and the number of cases, based on tabulations of individual medical records, are as follows:

	Number of cases	*Rate*
1942	159	1.56
1943	134	1.11
1944	115	1.34
1945	85	1.19

MIDDLE EAST

As the number of troops on duty in the Middle East was not large, the rates were not highly significant. Climatic conditions were variable, and exposure to contagion, as reflected by the mortality in the local population, was high. The heat in Iran was excessive and made it impossible for troops on duty to get normal rest. The annual incidence rates per 1,000 average strength and the number of cases, based on tabulations of individual medical records, are as follows:

	Number of cases	*Rate*
1942	3	0.50
1943	47	.89
1944	50	1.08
1945	20	.72

FAR EAST

The number of cases of tuberculosis developing in the U.S. Army in Japan, between the date of initial occupation and the end of 1945, was very small. Only 24 cases were recorded, which yielded an annual rate of 0.24 per 1,000 per annum. The surgeon of the occupying forces, however, in a later report on tuberculosis in Japan, called attention to the prevalence of the disease in the native population, which suggested a correspondingly grave exposure of troops on duty in the islands. The annual mortality from tuberculosis in Japan was recorded, on the basis of figures obtained from the Japanese Anti-Tuberculosis Association, as ranging from 209 per 100,000 in 1941 to 282 per 100,000 in 1946. In view of the known great deficiency of beds for the care of the tuberculous in Japan, it may be assumed that large

numbers of open cases were scattered through Japanese communities without isolation or care.

During 1946, the hospital a[illegible]on rate for tuberculosis, as recorded in the theater, rose notably. Pa[illegible]his rise, however, particularly in the months of June, July, and Augu[illegible], was the result of rapid discovery of cases in Philippine troops on discharge from the U.S. Army. As the report indicates, however, rates considerably higher than those for troops in the United States prevailed in the theater at the close of 1946.

It was evident that the problem of tuberculosis in troops on duty in the Far East was serious. It was complicated by the presence of numerous Philippine soldiers among the occupying troops, a group with a relatively high incidence of tuberculosis as compared with those recruited in the United States. Continual attention must be given in the future to the factor of contagion in this region.

Part III. Particular Aspects of the Disease

EXTRAPULMONARY TUBERCULOSIS

Extrapulmonary tuberculosis may be a complication of pulmonary tuberculosis, or may occur in the absence of significant pulmonary disease. Figures indicating its prevalence in the general population are based on mortality records, rather than incidence during life, and indicate that about 10 percent of all fatal tuberculosis is predominantly nonpulmonary. In the approximate order of frequency of involvement are the urogenital tract, bones, lymph nodes, serous membranes, and other sites, such as the adrenal glands. In many cases, the contributing, final cause of death is miliary tuberculosis or tuberculous meningitis. The position of intestinal tuberculosis is indeterminate. In the great majority of cases, this form is simply a complication of pulmonary tuberculosis, but not infrequently its manifestations are so severe that they dominate the clinical picture, so that death is reported as due to intestinal, rather than to pulmonary, disease.

Nonpulmonary tuberculosis, the scrofula of ancient times, is most prevalent among primitive peoples and those whose hygienic environment is poor. It is also frequent where the alimentary intake of tubercle bacilli is common, as in localities where bovine tuberculosis is widespread and milk is not pasteurized.

Troops of the U.S. Army met both of these conditions overseas. Among the natives in the Pacific islands the scrofulous types of tuberculosis were relatively common, while bovine tuberculosis was frequent in the British Isles and continental Europe. The reasons for prevalence of nonpulmonary tuberculosis in primitive cultures are complex, including racial factors as well as habits and customs. In the United States, as a result of a combination of circumstances, nonpulmonary tuberculosis is more frequent in Ne-

groes and Indians than in white people, and this fact held for troops of these races.

The contagion of nonpulmonary tuberculosis, even more than of pulmonary tuberculosis, depends on the closeness of contact. There was no reason to believe that the contacts of American troops with a population in which nonpulmonary tuberculosis is more common than in the United States would lead to a higher incidence of this type of tuberculosis than normally prevails in our population. Such a result would imply prolonged intimate contacts, as by adoption of primitive customs, such as eating from a common bowl or careless skin contacts with open ulcers or draining sinuses of infected persons.

On the other hand, infection from raw milk, particularly in the British Isles, was clearly recognized as a danger from the outset, and precautions against it during our troops' residence overseas were taken early.

An observation made in the course of military operations in World War I is pertinent.[36] The American pathologist, Maj. Eugene L. Opie, MC, stationed in France, called attention to the fact that calcified tuberculosis of primary infection was very frequently observed in the mesenteric lymph nodes of British troops, indicating an alimentary origin, presumably by ingesting infected milk. In the bodies of Americans, in marked contrast, primary infections were almost always in the lungs or tracheobronchial lymph nodes, and so presumably had been acquired by inhalation of tubercle bacilli.

By far the greatest amount of the milk consumed on Army posts overseas was dried pasteurized milk shipped from the United States. There was always, however, some danger from milk from private sources. In the early months overseas, some of the Red Cross canteens served local milk, the safety of which was not assured. Later, about February 1943, this practice was stopped entirely. The U.S. Army Veterinary Corps in the British Isles was constantly on the alert for danger. Up to July 1942, the U.S. Army was on the British ration, which included milk from certain approved sources. The Veterinary Corps came to the conclusion that, in spite of a variety of precautions, "there were too many hazards involved for its general use." Circulars Nos. 40 and 72, Headquarters, European Theater of Operations, dated 5 September and 10 November 1942, respectively, sharply restricted purchase of milk and imposed rigid standards with respect to the source. Relatively few sources satisfied these standards; consequently, after the early months, little British milk was consumed in the official ration. Consumption of raw milk by soldiers in the homes of friends could not be so well controlled, and some infection may have been transmitted in this way, but the total hazard was not great, as relatively little milk was available to the general population.

[36] Opie, E. L.: First Infection With Tuberculosis By Way of the Intestinal Tract. Am. Rev. Tuberc. 4: 641-648, November 1920.

Since tuberculosis is a disease of slow development, it is not easy to determine the source of infection in a given case. Disease acquired overseas may not become manifest for several years. Therefore, it is not known how much nonpulmonary tuberculosis observed in American troops originated there. It can only be said that the incidence (of forms other than pleuritis) showed no rise before the end of the war. The overall rates per 1,000 for the total Army for all forms of nonpulmonary tuberculosis, including tuberculosis of the larynx, trachea, bronchi, and pleura, for the years 1942, 1943, 1944, and 1945, were 0.13, 0.13, 0.17, and 0.23, respectively. Tuberculosis of the pleura is of special interest and is considered under the next heading and elsewhere in this account. Figures for the incidence of the other more common forms of nonpulmonary tuberculosis are presented in table 49.

TABLE 49.—*Incidence of nonpulmonary tuberculosis (excludes pleural tuberculosis) in the U.S. Army, 1942–45*

[Preliminary data based on sample tabulations of individual medical records]
[Rate expressed as number of cases per annum per 1,000 average strength]

Type	1942–45		1942		1943		1944		1945	
	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate
Genitourinary	674	0.03	50	0.02	199	0.03	210	0.03	215	0.03
Bones or joints	673	.03	100	.03	174	.03	194	.02	205	.03
External lymph nodes	586	.02	19	.01	224	.03	168	.02	175	.02
Skin	140	.01	5	.00	9	.00	36	.00	90	.01
Generalized miliary	133	.01	22	.01	48	.01	53	.01	10	.00
Meningitis	113	.01	19	.01	23	.00	56	.01	45	.01
Other [1]	928	.04	214	.07	242	.04	242	.03	230	.03

[1] Excludes tuberculosis of trachea and of bronchi in 1942 and 1943. During 1942–43, these two conditions were coded to pulmonary tuberculosis. In 1944 and 1945 there were 30 and 45 cases, respectively, which have been included in the "Other" category.

Differences in incidence overseas and incidence in the Zone of Interior were not significant, and accordingly combined figures for the total Army are given. The total amount of nonpulmonary tuberculosis, other than tuberculous pleuritis, was between 5 and 15 percent of all tuberculosis reported each year, a figure approximately the same as that for the civilian population. It should be noted that the methods of exclusion of nonpulmonary tuberculosis at induction were inferior to the X-ray procedure for detection of pulmonary tuberculosis. It became evident in retrospect that small lesions of the epididymis not infrequently escaped notice, and tuberculous superficial lymph nodes were also not conspicuous enough in many instances to be noted in the course of the usual rapid induction examination. Tuberculosis of the kidney was frequently evident on the basis of symptoms, history, or presence of pus in the urine, but some cases in an early stage were certainly undetected.

Racial differences with respect to nonpulmonary tuberculosis are discussed in the section on "Mortality From Tuberculosis." Aronson's studies [37] indicated that urogenital tuberculosis was more common in the white race, and tuberculosis of the lymph nodes, of the serous membranes, and of the bones was more common in Negroes.

PLEURISY WITH EFFUSION

Special interest is attached to the subject of tuberculous pleurisy with effusion, because of the indications discovered by Canadian medical officers that this form of tuberculosis in soldiers was a manifestation of recent primary tuberculosis in adult life, occurring with particular frequency in troops from parts of Canada with a low rate of exposure. Figures for the U.S. Army are more difficult to analyze in this respect than those for the Canadian Army, but there are some indications that a similar phenomenon occurred (pp. 403–405).

The medical treatment of pleurisy with effusion in the Army was variable. There was a tendency, particularly in oversea theaters, where demand for personnel was critical, to return men to duty after complete absorption of fluid and a period of hospital convalescence and rest.[38] In an appreciable number of cases of frank pulmonary tuberculosis that developed in the Army, clinical history disclosed a previous attack of pleurisy with effusion. In the Zone of Interior, the medical rule that pleurisy with effusion should be considered tuberculous if no other etiology could be proved was generally, although not invariably, followed, and many soldiers with effusion were sent to the Army hospitals used as tuberculosis centers and ultimately were discharged on certificate of disability as tuberculous. Clarification of procedure was brought about by TB MED (War Department Technical Bulletin) 71, dated 28 July 1944, and Change 1, dated 26 November 1946, in which the tuberculous nature of the disease was emphasized, instructions for diagnosis given, and principles for disposition set forth.

In 1942 and 1943, tuberculosis of the pleura was coded with pulmonary tuberculosis, with pleurisy as an associated disease. In 1944 and 1945, separate specific accounting was made of clearly diagnosed tuberculosis of the pleura and serofibrinous pleuritis of undemonstrated origin (table 50). The figures for these 2 years may therefore be used as suitable for comparing pleurisy with effusion with pulmonary tuberculosis, and the occurrence of pleurisy with effusion in troops overseas and in the United States.

It will be noted that the rate was appreciably higher in troops overseas than in those in the United States, where, it will be recalled, the admission rate for pulmonary tuberculosis was higher than in troops overseas (chart 18). However, great significance should not be attached to this apparent

[37] Aronson, J. D.: The Occurrence and Anatomic Characteristics of Fatal Tuberculosis in the U.S. Army During World War II. Mil. Surgeon 99: 491–503, November 1946.

[38] See footnote 29, p. 356.

discrepancy. The advent of pleurisy with effusion is generally sudden and dramatic with fever, pain, and other symptoms; the diagnosis, therefore, is relatively early and easy. Pulmonary tuberculous infiltration, on the other hand, is usually insidious in origin and diagnosis on a symptomatic basis, relatively late. It is quite reasonable to suppose that almost all of the serofibrinous pleurisy developing overseas was diagnosed there, whereas pulmonary tuberculosis acquired overseas in many instances was not detected until the return of the afflicted soldiers to the United States.

TABLE 50.—*Incidence of tuberculosis of pleura and serofibrinous pleuritis in the U.S. Army, 1944–45*

[Rate expressed as number of cases per annum per 1,000 average strength]

Category	Total Army	Continental United States	Outside continental United States
1944			
Tuberculosis of pleura	391	75	316
Serofibrinous pleuritis	3, 320	1, 500	1, 820
Total cases	3, 711	1, 575	2, 136
Total rate	0. 48	0. 40	0. 56
1945			
Tuberculosis of pleura	745	160	585
Serofibrinous pleuritis	2, 520	900	1, 620
Total cases	3, 265	1, 060	2, 205
Total rate	0. 44	0. 36	0. 50

All clinical experience indicates that the prognosis of cases of pleurisy with effusion, even without radiologically demonstrable pulmonary infiltration, is doubtful for at least 5 years. Texts and articles on the subject, in general, emphasize the fact that 25 to 50 percent of the cases of effusion inadequately treated, that is, not subjected to a period of rest of several months following absorption of the fluid, develop pulmonary tuberculosis within 5 years; thereafter, the incidence is like that in the general population of corresponding age.[39] The Army figures cannot be expected to reveal the total incidence of pulmonary tuberculosis developing in cases of pleurisy with effusion, for the critical 5-year period had only commenced in the majority of cases when demobilization began. It is possible that men who had had short attacks of pleurisy with effusion and were returned to duty with-

[39] (1) Thompson, B. C.: Pathogenesis of Pleurisy With Effusion; A Clinical, Epidemiological and Follow-up Study of 190 Cases. Am. Rev. Tuberc. 54: 349-363, October-November 1946. (2) Thompson, B. C.: Prognosis of Primary Pleurisy With Effusion. Brit. M.J. 1: 487–488, 12 Apr. 1947.

out residua, and ultimately discharged from the Army with negative X-ray films of the chest or no anomaly other than a costal diaphragmatic adhesion, may yet develop pulmonary tuberculosis as a result of the infection manifested originally only by the pleurisy. Care and compensation in these cases will be adjudication problems for the future.

As has been pointed out, in the various theaters the rate of admission for serofibrinous pleurisy in the Army was generally 25 to 30 percent of the rate of admission for pulmonary tuberculosis. In view of the probable tuberculous nature of the great majority of cases of effusion in which tuberculosis could not be unequivocally diagnosed by laboratory methods, it might seem appropriate to add the admissions of serofibrinous pleurisy to those for pulmonary tuberculosis to arrive at a true rate for the latter. This would not be accurate, however, as there would be a not insignificant duplication of cases. Men with a diagnosis of pleurisy with effusion in the admission records who returned to duty after recovery were subsequently, in an undetermined number of cases, given another diagnosis, and entered in the medical statistics of the Army as patients with pulmonary tuberculosis.

In summary, it appears warranted to believe that tuberculous pleurisy did occur more frequently in troops serving overseas than in those who never left the United States, and it seems reasonable, even with due allowance for greater physical strain and other factors that might be pertinent, to attribute the greater frequency, as did the Canadians, to the greater exposure overseas, where civilian populations were more heavily infected than in the United States. Much further research, taking into account the age and home residence of soldiers who developed tuberculous pleurisy with effusion, will be needed to support the Canadian view that the majority of cases of effusion represented recent primary tuberculous infections.

The American experience also indicates the necessity for a long-range view of the prognosis of pleurisy with effusion, with recognition not merely of immediate necessities for manpower, but also the questionable prognosis in the long run, of men seemingly recovering without residua and returned to military duty.

SPONTANEOUS PNEUMOTHORAX

The view once prevailed that the great majority of cases of spontaneous pneumothorax were complications of pulmonary tuberculosis. In 1932, in his textbook on tuberculosis, Fishberg[40] expressed the general opinion that 80 percent of cases were in that category. Subsequent investigation showed spontaneous pneumothorax to be not uncommonly an independent development.[41] Such, as seen in the Army, it was usually found to be.

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[40] Fishberg, Maurice: Pulmonary Tuberculosis. Volume I. Etiology, Pathogenesis, Symptomatology, Roentgenology, Clinical Forms. 4th edition. Philadelphia: Lea & Febiger, 1932.

[41] For a study of 58 cases, bibliography, and discussion of pathogenesis see Ornstein, G. G., and Lercher, L.: Spontaneous Pneumothorax in Apparently Healthy Individuals. Clinical Study of Fifty-eight Cases With a Discussion of the Pathogenesis. Quart. Bull., Sea View Hosp. 7: 149-187, April 1942.

During the years 1942 to 1945, inclusive, 3,831 admissions to Army hospitals for spontaneous pneumothorax were recorded. The great majority were nontuberculous. This number, in a total of approximately 11 million men, represented about 1 case per 2,700 men in the cumulative experience of 4 years.

The incidence of spontaneous pneumothorax, as indicated by rates of admission and readmission for the continental United States and the oversea theaters during the 4 war years, is presented in table 51.

TABLE 51.—*Admissions and readmissions for spontaneous pneumothorax in the U.S. Army, by area and year of admission. 1942–45*

[Preliminary data based on sample tabulations of individual medical records]
[Rate expressed as number of new admissions per annum per 1,000 average strength]

Year and area of admission	Admissions		Readmissions
	Number	Rate	
1942			
Continental United States	384	0. 14	8
Outside continental United States	56	. 10	----------
Total Army	440	0. 14	8
1943			
Continental United States	930	0. 18	25
Outside continental United States	163	. 10	2
Total Army	1, 093	0. 16	27
1944			
Continental United States	805	0. 20	15
Outside continental United States	353	. 09	6
Total Army	1, 158	0. 15	21
1945			
Continental United States	585	0. 20	20
Outside continental United States	555	. 12	----------
Total Army	1, 140	0. 15	20
1942–45			
Continental United States	2, 704	0. 18	68
Outside continental United States	1, 127	. 11	8
Total Army	3, 831	0. 15	76

As the figures show, the admission rate overseas was consistently less than in the United States, a fact perhaps merely indicating that a soldier predisposed to spontaneous pneumothorax by anatomical defect or other cause was likely to develop it in his early Army training if at all.

In 1943, when there were 930 hospital admissions in the continental United States for this cause, and medical officers were in doubt as to proper treatment, the Subcommittee on Tuberculosis, National Research Council, was asked to study the subject and make recommendations on treatment. This request resulted in the publication of a document by the Office of Medical Information of the Division of Medical Sciences, National Research Council, which was given wide distribution in U.S. Army medical installations.[42] At the same time, an article was published in the *Bulletin of the U.S. Army Medical Department* calling attention to the frequency of spontaneous pneumothorax, the deficiencies in present-day treatment, the need for individualization in treatment, and the dangers inherent in the several methods available.[43] The note pointed out that up to the time of its writing, spontaneous pneumothorax had been considered of sufficient gravity to warrant separation from the service in 15 percent of cases and that the average duration of hospitalization for this condition had been 40 days.

In the document published by the National Research Council, a useful classification was given, with pertinent material on diagnosis and prognosis. The relationship to bullae in the lung was indicated, although it is known that very frequently such bullae cannot be demonstrated during life by any radiological or other method. Conservatism in treatment was recommended. Prompt hospitalization was required, with avoidance of physical effort. Special warning was given against transportation by air. It was noted that the air in the pleural space is absorbed spontaneously in most cases within a few weeks. Aspiration at short intervals may be desirable for a few days at the start.

The chief problem in spontaneous pneumothorax in the Army was recurrence. Waring's review of the literature indicated recurrence in 10 to 20 percent of cases. Most of the discharges from the Army for spontaneous pneumothorax were for recurrence or persistence. In many of these cases, various methods of obliterating the pleural space to prevent recurrence were tried. Two that met with some success were injection of whole blood from the patient and insufflation of powdered talc. In Waring's report, the dan-

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[42] Waring, J. J.: Spontaneous Pneumothorax. Office of Medical Information, Division of Medical Sciences, National Research Council, July 1944.

[43] (1) Pease, P. P., Steuer, L. G., and Chapman, A. S.: Spontaneous Pneumothorax in Soldiers. Bull. U.S. Army M. Dept. No. 82: 102 107, November 1944. (2) Spontaneous Pneumothorax. Bull. U.S. Army M. Dept. No. 82: 29, November 1944.

gers of induced "chemical pleuritis," particularly uncontrollable thickening of the pleura, were discussed.[44]

In general, the Army experience indicated that spontaneous pneumothorax is a not uncommon phenomenon; that it is favored by exertion, but may occur independently of any physical strain; that recurrence is not infrequent and may necessitate discharge; and that individualization is necessary in treatment. Account was taken of its importance for induction by the requirement, in late revisions of Army Regulations pertaining to physical standards, including Mobilization Regulations, that men with a verified history of spontaneous pneumothorax within 3 years, or recurrent spontaneous pneumothorax at any time, should be excluded from service.

MORTALITY FROM TUBERCULOSIS

Figures on mortality from tuberculosis in the Army are not highly significant. Active tuberculosis was rarely compatible with return to active duty, and accordingly Army Regulations required discharge of patients after diagnosis and such initial hospitalization as was necessary to insure the best results in a Veterans' Administration hospital or civilian hospital after discharge. It was specifically stated in AR (Army Regulations) 615–361, 14 May 1947, however, that moribund cases were not to be discharged. Hence, the deaths that occurred from tuberculosis in the Army represented cases in which the disease was far advanced on discovery, acute in its progression, or first diagnosed and hospitalized in regions where early evacuation was not possible.

During World War II, the annual mortality from tuberculosis in the Army averaged about 3 per 100,000 while in the civilian population of corresponding age the rate was about 50 per 100,000. The corresponding figures for World War I were 67 in the military population and over 150 per 100,000 in the civilian population.

The incidence and character of fatal tuberculosis in the Army formed the subject of a special investigation,[45] in which comparison was made of the pathology of the disease in white and in Negro troops. In general, the evidence favored the view that the Negro race has a lower inherent resistance to tuberculosis than the white race, for, in spite of approximate uniformity of environment, Negro troops, representing only 10 percent of the population of the Army, contributed 43.4 percent of the deaths from tuberculosis. Unusual differences were not observed in the extent or character of tuberculosis

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44 (1) See footnote 42, p. 374. (2) For a further discussion of the treatment of spontaneous pneumothorax see Blades, Brian B., Carter, B. Noland, and DeBakey, Michael E.: Surgical Aspects of Diseases of the Chest. *In* Medical Department, United States Army. Surgery in World War II. Thoracic Surgery. Volume II, ch. X. [In preparation]—J. B. C., Jr.

45 See footnote 37, p. 370.

in the different organs in the two races. Highly destructive tuberculosis was somewhat more frequent in the lungs of Negro than in white troops, and healed tuberculosis was a more common incidental finding in white than in Negro troops. In white soldiers, the central nervous system and genitourinary organs were more commonly affected than in Negro troops, and in the latter there was higher incidence of tuberculosis of lymph nodes, bones, and peritoneum. Tuberculous meningitis was slightly more common in Negro than in white soldiers.

In both races, the duration of the disease appeared remarkably short as compared with that in the civilian population. The reason for this has already been given; namely, the likelihood of discharge of chronic cases before death could occur. A relatively high incidence of fatal tuberculosis occurred in recovered prisoners of war who had suffered privations for many months in prison camps overseas.

Although the mortality from tuberculosis among troops actually in service does not yield statistically significant figures, such figures can be obtained by combining the mortality totals for the military population in service and discharged. Figures so compiled indicate that a steady rise has occurred in the mortality from tuberculosis in the group of men accepted for service in the Army since the beginning of World War II.[46] During 1942, the combined rate for troops in service and troops previously discharged was approximately 3 per 100,000 per annum; thereafter, it rose to 6 in 1943, 10 in 1944, and 12 in 1945.

This steady rise indicates that tuberculosis continued to increase with time in a group generally well screened by X-ray examination before induction. There is reason to believe that the rise was due to several factors, including slow and ultimately fatal development of previously unrecognized disease present at the time of acceptance and the acquisition of infection from outside sources during the years of military service. For comparison, it may be noted that during the years under consideration the tuberculosis death rate for the civilian population of corresponding age remained, with minor fluctuations, at approximately 52. Thus, the rate for the screened population was far below that of the corresponding unscreened population, which included those screened out because of tuberculosis. The rate which the disease will ultimately attain will depend on many factors, including measures against tuberculosis in the general population and special measures for veterans taken by the Veterans' Administration.

Eight hundred and six deaths from tuberculosis were recorded in Army personnel from 1942 to 1945, inclusive (table 52).

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[46] Long, E. R.: Tuberculosis in a Screened Population. Am. Rev. Tuberc. 54: 319-320, September 1946.

TABLE 52.—*Deaths due to tuberculosis in the U.S. Army, by broad area of admission, rank, sex, race, and year of death, 1942–45*

[Preliminary data based on tabulations of individual medical records]
[Rate expressed as number of deaths per annum per 100,000 average strength]

Year of death and area of admission	Total Army		Male personnel										Female personnel	
			Total		Officers		Enlisted men							
							Total [1]		Non-Negro		Negro			
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
1942														
Continental United States	92	3.46	91	3.44	1	0.57	90	3.65	58	2.53	32	17.94	1	7.89
Outside continental United States	15	2.56	15	2.57	1	2.76	14	2.56	12	2.30	2	7.66	.....	0
Total Army	107	3.30	106	3.28	2	0.94	104	3.45	70	2.49	34	16.63	1	6.52
1943														
Continental United States	146	2.82	145	2.83	4	0.96	141	3.00	73	1.70	68	16.62	1	1.63
Outside continental United States	46	2.73	46	2.74	.....	0	46	2.97	35	2.45	11	8.99	.....	0
Total Army	192	2.79	191	2.81	4	0.74	187	2.99	108	1.89	79	14.86	1	1.40
1944														
Continental United States	89	2.24	89	2.28	7	1.72	82	2.35	40	1.26	38	12.12	.....	0
Outside continental United States	112	2.93	112	2.96	2	.66	110	3.15	58	1.85	49	14.09	.....	0
Total Army	201	2.58	201	2.61	9	1.27	192	2.75	98	1.55	87	13.16	.....	0
1945														
Continental United States	63	2.11	61	2.12	7	1.63	54	2.20	26	1.15	26	13.17	2	1.99
Outside continental United States	243	5.46	243	5.51	13	3.69	230	5.66	134	3.69	82	19.05	.....	0
Total Army	306	4.12	304	4.17	20	2.56	284	4.36	160	2.72	108	17.20	2	1.45
1942–45														
Continental United States	390	2.64	386	2.65	19	1.33	367	2.80	197	1.64	164	14.93	4	1.63
Outside continental United States	[2] 416	3.95	416	3.98	16	1.96	400	4.15	239	2.74	144	15.54	.....	0
Total Army	806	3.18	802	3.21	35	1.56	767	3.37	436	2.10	308	15.21	4	1.23

[1] Because it includes "race unknown," the total number of deaths among enlisted men may be larger than the sum of the figures shown for the separate racial categories.

[2] Of the total deaths in 1942–45 that were admitted overseas approximately 52 percent had been evacuated to the Zone of Interior during 1942–45. By year of deaths, the proportions were: 7 percent for 1942, 37 percent for 1943, 54 percent for 1944, and 57 percent for 1945.

Part IV. Hospitalization and Treatment in the Zone of Interior

GENERAL PRINCIPLES OF EVACUATION

For accounts of evacuation of tuberculous patients from the different theaters, the reader is referred to sections of this chapter in which the experience of each theater is described. In the early days of World War II, evacuation was by transport, for neither hospital ships nor planes were available. The best facilities available on troopships were accorded tuberculous patients, but this mode of transfer to the Zone of Interior had obvious disadvantages. Quarters were crowded, nursing attention was minimal, facilities for proper care were inadequate, and suitable provision could not be made for isolation.

In contrast, when hospital ships became available in sufficient numbers, the transfer of tuberculous patients from oversea theaters was handled in a creditable manner. As a rule, quarters designed for contagious diseases were used, so that isolation was feasible, and both nursing and medical care were more nearly adequate. Hospital ships had good laboratories and suitable X-ray apparatus and, as a general rule, a sufficient number of nurses. Port surgeons issued directives in early 1945 covering the care of patients en route and the sanitary precautions to be taken.

Early in 1945, when the number of tuberculous patients returning from overseas was fairly high, attention was drawn to the fact that convoys were often so large that the surface water, which was pumped into ships for bathing and other purposes, was contaminated to a noticeable degree by sewage from the ships of the convoys. Recognizing the fact that tubercle bacilli might be present in the discharges from tuberculous patients, and be unwittingly drawn into the water supply for scrubbing and deckwashing in rear ships of convoys, the Office of the Surgeon General forwarded a letter in March 1945 to the New York Port of Embarkation outlining principles to be followed to prevent this type of contamination. Suggestions from the Office of the Surgeon General, including a statement on general measures in the care of tuberculous patients en route, were embodied in Circular Letter No. 10 from the Port Surgeon, New York Port of Embarkation, 26 March 1945, entitled "Care of Tuberculous Patients During Water Transportation." This circular established important provisions for sputum control, emphasizing (1) education of patients, (2) use of gauze for cough, (3) use of sputum cups, and (4) decontamination of quarters following their use by tuberculous patients, as well as the principles of isolation and proper care of utensils and laundry.

It was required that gauze, tissue, sputum cups, and bags containing gauze and other contaminated material be destroyed each day. It was recommended that if burning, the most satisfactory method of disposal, was not

practicable, the material to be destroyed should be placed in cloth bags of appropriate size to be weighted and sunk. It was pointed out that this infectious material should not be cast overboard indiscriminately to possibly contaminate the water pumped into the other ships.

The danger from indiscriminate use of sea water around convoys does not however appear to have been great, for tests for the presence of sewage carried out at the rear of large convoys failed to reveal any great amount of contamination, but the effort was considered worthwhile from the standpoint of public health practice.

Circular Letter No. 10 emphasized rest for the patient, avoidance of all unnecessary activity, proper ventilation of quarters, and an adequate diet. It was indicated that a diet including liberal quantities of milk, eggs, butter, orange juice, tomato juice, and meat was practicable on board ship. Ordinarily, the standard diet of the ship appeared suitable if supplemented by midmorning and midafternoon feedings of orange juice, tomato juice, or milk.

Not infrequently it was necessary to administer pneumothorax en route to patients in whom this form of therapy had been instituted overseas. Qualified medical personnel were not always available for this purpose, but in the late months of the war every effort was made to insure the presence on each hospital ship of a medical officer trained in the administration of pneumothorax.

Airplane transportation ultimately proved most desirable for the majority of tuberculous patients. It was suitable for all those with early disease, and for the majority with moderately advanced illness. Patients with large tension cavities and those with artificial pneumothorax were usually not transported by air. A specific study of the effects of air travel on patients with tuberculosis was made by the Army Air Forces. The Office of the Air Surgeon, on request for an opinion, sent the following communication to the Office of the Surgeon General:[47]

> With respect to transportation of tuberculous cases, experience gathered during the past 24 months has shown that patients whose medical condition warrants movement suffer less shock and embarrassment when moved by air than by other means of transportation. Patients with active pulmonary tuberculosis have been flown for long distances at altitudes of 20,000 feet or more (with constant use of oxygen) without ill effect. Air movement of patients is routinely carried on at altitudes between 2,000 and 8,000 feet, except when weather, terrain, or military operations force the planes to higher altitudes.
>
> Sound medical judgment of the responsible medical officer in each individual case must remain the final answer as to suitability for movement of tuberculous patients.

A special report on the transportation by air of tuberculous patients was prepared by the Section for Research on Minimal Tuberculosis, U.S. Army

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47 Transmittal Sheet, Col. A. H. Schwichtenberg, MC, Air Liaison Officer to The Surgeon General, to The Air Surgeon, 20 May 1944, subject: Evacuation of Tuberculous Patients by Air, first indorsement thereto, dated 18 July 1944.

Medical Research and Development Board and University of Colorado Medical Center, at Fitzsimons General Hospital.[48]

Transportation of patients with artificial pneumothorax had always to be given serious consideration.[49] Intrapleural gas doubles in volume at 18,000 feet, and proportionate increases take place at lower altitudes. The excessive expansion at high altitudes might be expected to lead to tearing of adhesions and other untoward results. The problem was one of importance not only in oversea transport, which occasionally required flight at high altitudes to avoid storms and enemy interference, but also in the Zone of Interior, for large numbers of patients were flown to Fitzsimons General Hospital situated at an altitude of 5,000 feet in Colorado and Bruns General Hospital situated at an altitude of 7,000 feet in Santa Fe, N. Mex. Ordinarily, transportation of tuberculous and other patients was accomplished at the usual altitudes of commercial flying.

As the war progressed and the return movements of patients reached large dimensions, it was found that air transport, with proper safeguards, was without hazard. It was so well developed by the end of the war that it was considered the method of choice wherever practicable. Most important, it insured early definitive care in the United States, for such treatment, including collapse therapy, in many cases was not initiated in the theater but left to the judgment of the hospital charged with long-term treatment of the patient.

On such flights, it was essential to provide, against possible emergency, adequate nursing care and technical medical assistance. Ordinarily, a physician did not accompany a flight, but a trained nurse was always present, and the total time spent between the oversea theater and the Zone of Interior was short. As in transportation by water, proper isolation had to be insured. Occasionally, tuberculosus patients were sent on the same plane with other patients, but whenever feasible an entire plane was reserved for their use. This frequently meant holding patients at hospitals of embarkation overseas for some days until a sufficient number had gathered.

The Office of the Surgeon General sent a civilian consultant, Dr. James J. Waring of Denver, Colo., to the San Francisco Port of Embarkation and Hamilton Field, Calif., to advise on transportation by air and by water of patients from the Pacific areas. Air transport from these areas was particularly important because of the great distances involved. From July to December 1944, about 6,000 patients were flown from the Pacific areas to Hamilton Field, and of these 140 were tuberculous.

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[48] Roper, W. H., and Waring, J. J.: Air Evacuation of Tuberculous Military Patients. Am. Rev. Tuberc. 61: 678–689, May 1950.

[49] (1) Minutes, Subcommittees on Tuberculosis, Committee on Medicine, National Research Council, 21 Feb. 1942 and 10 June 1944. (2) Bridge, E. R., and Bridge, E. V.: Effect of Altitude on Abnormal Accumulations of Air in the Chest. Am. Rev. Tuberc. 51: 532–537, June 1945. (3) Tuberculosis Abstracts, National Tuberculosis Association 19, No. 10, October 1946. (4) Duff, F. L.: Physical Factors in Air Evacuation. Bull. U.S. Army M. Dept. 7: 860–868, October 1947. (5) Air Transport of Tuberculous Patients. Bull. U.S. Army M. Dept. No. 87: 8, April 1945.

In the United States, tuberculous patients were delivered at debarkation hospitals, whether arriving by ship or by air, and after appropriate triage were transferred for further care to Fitzsimons and Bruns General Hospitals, a large number of them by air. Hospital commanders made every effort to forward tuberculous patients in plane and carload lots to avoid exposure of nontuberculous patients.

The final conclusion as a result of this experience was that airplane transportation was most appropriate whenever it was practical. For cases not suitable for air transport, hospital ships rather than transports should be used. Emphasis should be laid on proper isolation of cases, on safety, sanitary precautions, and avoidance of emergency. Finally, experience showed that medical officers with training in tuberculosis should be assigned to duty at embarkation hospitals overseas and debarkation hospitals in the Zone of Interior to insure proper care throughout the course of transfer.

SPECIALTY CENTERS FOR TREATMENT

Discovery and treatment of tuberculosis in hospitals overseas has been described for the several theaters. Hospitals at stations with a troop strength of over 5,000 men were authorized to discharge patients with tuberculosis on certificate of disability, and a large proportion of the total number of certificates of disability for discharge for this cause were granted at station hospitals. In all cases of doubt, however, where the diagnosis could not be established in a station hospital, the patient concerned was sent to a general hospital. Many were sent to Fitzsimons General Hospital which was a center for treatment of tuberculosis throughout the entire period of the war and received the majority of commissioned officers and noncommissioned officers hospitalized for tuberculosis.[50]

In the course of the war, two other hospitals were made specialty centers for tuberculosis: Bruns General Hospital, and Moore General Hospital, Swannanoa, N.C. Bruns General Hospital, which was activated on 18 February 1943, was made a center in August 1944,[51] for the treatment of "patients requiring special evaluation or prolonged care in an Army hospital specializing in the treatment of tuberculosis." It had become necessary to supplement Fitzsimons General Hospital to provide care for the numerous patients with tuberculosis evacuated from overseas. It was directed [52] that, if male tuberculous enlisted personnel and officers whose homes were in the Eighth Service Command were evacuated from overseas, they were to be transferred from debarkation hospitals to Bruns General Hospital. Women were sent to Fitzsimons General Hospital. It may be noted incidentally that Bruns General Hospital, chosen for reasons of climate and availability, by happy coincidence was named after one of the Army's outstanding specialists in tuberculosis,

[50] War Department Circular No. 338, 18 Aug. 1944.
[51] War Department Circular No. 347, 25 Aug. 1944.
[52] See footnote 13, p. 337.

Col. Earl Harvey Bruns, MC, who had trained many medical officers during and after World War I and was for years after the war, Chief of Medical Service at Fitzsimons General Hospital.

The third specialty center for tuberculosis, Moore General Hospital, was established in the late months of the war, when many tuberculous patients were being found at separation centers.

The official annual reports for the three hospitals named, which are on file in the Office of the Surgeon General, give full details on the size of the medical and surgical staffs, the personnel changes that occurred during the war, the number of tuberculous patients treated, the types of therapy employed, and special problems encountered. At all hospitals, standard methods of therapy were employed, with principal emphasis on rest and the use of collapse measures in appropriate cases. The extent to which different collapse procedures were employed depended on the type of case, the special skills of the hospital staff, and the length of stay of patients. The frequency of collapse therapy was in inverse ratio to the length of stay in the hospital. Prior to 1946, except for a few special cases in which Promin (glucosulfone sodium) and Promizole (2-amino-5-sulfanilylthiazole) were employed, chemotherapy was not practiced in the Army. Subsequently, the Army participated actively in study of the treatment of tuberculosis with streptomycin.[53]

In addition to their function as treatment centers, the hospitals trained medical personnel for positions of responsibility overseas and in the Zone of Interior. Indeed, frequent changes in personnel, inevitable under the circumstances, interfered seriously with the efficiency of the treatment given.

Fitzsimons General Hospital.—Col. George F. Aycock, MC, was chief of medical service throughout the period covered by this history. Lt. Col. (later Col.) John B. Grow, MC, was chief of surgical service, and Maj. (later Lt. Col.) Richard H. Meade, MC, was assistant chief and later chief of the thoracic surgery section.

Cases of tuberculosis exceeded those of any other disease, since the chief purpose of the hospital was "to give treatment under [the] most favorable conditions to patients [suffering] with tuberculosis."[54] During 1942, 1,273 enlisted men were admitted to the tuberculosis section[55] and 106 officers including nurses were admitted for tuberculosis. At the end of the year, 800 enlisted men were under treatment. The practice was to retain cases of pulmonary or predominantly pulmonary tuberculosis on the medical service, and cases of genitourinary, bone, joint, and lymph node tuberculosis on the surgical service. Artificial pneumothorax and pneumoperitoneum were practiced on the medical service, and phrenic nerve operations, intrapleural pneumonolysis and extrapleural thoracoplasty, as well as less frequent operative proce-

[53] U.S. Veterans Administration: The Effect of Streptomycin Upon Pulmonary Tuberculosis. Preliminary Report of a Cooperative Study of 223 Patients by the Army, Navy and Veterans Administration. Am. Rev. Tuberc. 56: 485-507, December 1947.

[54] Army Regulations No. 40-600, 6 Oct. 1942.

[55] Personal communication, Executive Officer, Fitzsimons General Hospital, to Col. E. R. Long, MC, 19 Mar. 1947.

dures, were carried out on the surgical service, with return of patients to the medical service following convalescence. During 1942, 320 artificial pneumothoraces were induced and an additional 147 were continued after previous induction. Thus, more than a quarter of all the patients admitted were treated by pneumothorax. On the surgical service, 171 thoracoplasties, 187 pneumonolyses, and a small number of pneumonectomies and lobectomies were performed during 1942.

The report for 1942 indicates that 20 percent of all cases of tuberculosis had nonpulmonary tuberculous complications, of which tuberculous laryngitis, tuberculosis of the genitourinary tract, tuberculous enterocolitis, and tuberculosis of the bones were most common. Of nontuberculous complications, diabetes was most frequent. One-third of the cases under pneumothorax treatment developed pleural effusion, a figure that had held during several years of previous experience.

In 1943, there were marked fluctuations in admissions and discharges of tuberculous patients. The tuberculosis section remained the largest section on the medical service; 1,405 enlisted personnel were admitted. However, the census dropped sharply following publication of War Department Circular No. 109, 26 April 1943, which directed discharge to the Veterans' Administration of men unfit for military service and so abrogated the previous practice of holding patients for at least 6 months. During the year, there were 1,332 direct admissions of enlisted men for tuberculosis, and 634 tuberculous patients remained at the end of the year. There were 1,585 discharges from the section, chiefly on certificate of discharge for disability, and 65 deaths.

The proportions on different forms of collapse therapy were approximately as in the preceding year. There were 239 pneumothoraces initiated and 12,044 refills given. On the surgical service, 428 operations for tuberculosis were performed, including 180 thoracoplasty stages, 184 phrenic nerve operations, and 49 intrapleural pneumonolyses.

As in the preceding year, pleural effusion developed in 33 percent of the pneumothorax cases, usually (85 percent) serofibrinous, but occasionally (15 percent) purulent. Nonpulmonary tuberculous complications were of the same frequency and nature as before. Among nontuberculous complications, coccidioidomycosis was the most frequent, its incidence in the Army having notably increased as a result of desert maneuvers.

During 1943, with the longer progress of the war, there was a noteworthy increase in the number of officers admitted (277 males and 86 females). Of this number, 132 were discharged, chiefly by retirement.

In 1944, the number of admissions for tuberculosis (1,895) was somewhat larger than in preceding years. The number of cases given collapse therapy was somewhat smaller, and the number given pneumoperitoneum slightly larger, the indications for the latter therapy having become more clearly defined. Pneumoperitoneum was considered of value in those cases of tuberculosis in the exudative phase in which it was unwise to attempt pneumothorax,

as well as in cases with basal and perihilar excavation. A remarkable constancy was apparent in the incidence of pleural effusion as a complication of artificial pneumothorax, as it occurred in 32 percent as compared with 33 percent of cases in each of the preceding years.

In 1944, there was a sharp curtailment in the use of surgery; only 33 thoracoplasties were performed. This was due to the shorter average stay of patients, owing to the heavy demands on the hospital not only for cases of tuberculosis but also for other illness. During this year, however, 15 lobectomies were performed, the indications for this operation having become clearer within the preceding year. In general, cases with an excavated, but well-stabilized lesion, confined to one lobe, were considered most suitable for lobectomy.

During 1944, the number of cases in enlisted men evacuated from overseas, which had heretofore formed a substantial proportion of the total, decreased markedly, as a result of the designation of Bruns General Hospital as a center for such cases. However, the number of officers from both overseas and the Zone of Interior increased greatly, with 647 admissions (561 male and 86 female). There were 419 tuberculous officers discharged by retirement or other procedure.

A significant development during 1944 was the activation, in January, of the Section for Research on Minimal Tuberculosis. This section was developed by the Office of the Surgeon General on the advice of the Subcommittee on Tuberculosis, National Research Council. It was sponsored and supported financially by the Army Medical Research and Development Board. The subcommittee felt that the Army, with its large number of well-studied cases, afforded a unique opportunity for investigation of the prognosis of minimal tuberculosis and the reasons for the breakdown of small or incompletely stabilized lesions. A contract was drawn by the board with the School of Medicine, University of Colorado, Denver, located only a few miles from Fitzsimons General Hospital, and Dr. Waring, Professor of Medicine, School of Medicine, was designated as responsible investigator, with Colonel Aycock, Chief of Medical Service, Fitzsimons General Hospital, and Colonel Long as consultants. Capt. (later Maj.) William H. Roper, MC, formerly chief of the section for chest diseases at the Station Hospital, Fort Bragg, N.C., was assigned, through Seventh Service Command Headquarters, to Fitzsimons General Hospital for the detailed prosecution of the investigation, which was to be based on an intimate study of the history and progress of 1,000 cases of tuberculosis of minimal extent.

By the end of the year, 400 cases had been studied with care. In June 1946, the final number was 1,108. This number included 648 cases of active and 350 cases of inactive minimal parenchymal disease; in addition, there were 110 cases of pleural effusion presumed or proved to be tuberculous in origin. In 397 cases, the investigation included an intensive psychiatric examination to determine the influence of emotional and personality factors

upon breakdown with tuberculosis. This examination was conducted by Dr. John M. Lyon, Department of Psychiatry, School of Medicine, University of Colorado.[56]

During 1945, the tuberculosis section of Fitzsimons General Hospital was more active than in any preceding year. There were 2,474 admissions to the enlisted men's section. The average number of patients was greater, and collapse therapy was carried out on a larger scale than heretofore. There were 448 initial pneumothoraces, and the total number of refills, in spite of the relatively short duration of residence that was necessary in order to accommodate new cases, was 11,265. Pneumoperitoneum was induced in 136 cases. The surgical service there were 3 pneumonectomies, 34 lobectomies, and 7 partial lobectomies for tuberculosis.

During the 4 years of the war, Fitzsimons General Hospital admitted more than 8,100 patients with tuberculosis. The morale of both staff and patients was excellent, and the treatment was equal to that in the best civilian hospitals in the country. In view of the usual early transfer of patients, rehabilitation measures were not extensively employed, although there was provision for occupational therapy. Long before the maximum results of treatment could be attained, regulations required discharge of patients to the Veterans' Administration or other institutions for care. Results in terms of cases arrested or improved, or stationary or unimproved, cannot, therefore, be given for evaluation or comparison with results at other hospitals. Only through careful followup of cases handled by the Veterans' Administration will it be possible to determine the effectiveness of several months of treatment at Fitzsimons General Hospital in bringing about lasting arrest of cases.

The pathology service, under Col. Hugh W. Mahon, MC, made careful studies of necropsies and maintained a series of records that were of unusual value, because of the wealth of photographic reproductions included. The majority coming to autopsy were chronic cases, fibroulcerative in character, although there were some more acute cases, including a number with fulminant tuberculous meningitis. In general, post mortem observations made in the Army were not significantly different from those in large civilian hospitals and sanatoriums for tuberculosis.

Discharge and retirement constituted a problem that was, at times, difficult. Since patients could not be held for the many months required for complete arrest of the disease, discharge had to be effected on the basis of disability, with such compensatory benefits as accrued. In cases of advanced tuberculosis, no problem was involved. In cases of early tuberculosis of minimal extent, apparently well scarred after a few months of treatment, the appropriate course generally appeared to be to discharge patients on the basis of disability, even though no symptoms persisted and prognosis was excellent. This disposition also appeared generally indicated in cases of

[56] Waring, J. J., and Roper, W. H.: Minimal Pulmonary Tuberculosis in Military Personnel: World War II. Am. Rev. Tuberc. 75: 1-40, January 1957.

healed pleural effusion in which all fluid was absorbed, no pulmonary infiltration was evident, and exclusion studies indicated that the process was presumptively tuberculous. Since tuberculosis is a disease prone to relapse if a proper regimen is not followed, it was necessary to consider such cases as potentially active for some years. Similar considerations applied to tuberculosis of lymph nodes when nodes with doubtfully active tuberculous lesions had been removed and tuberculous foci were not found elsewhere in the body. Such cases were finally resolved in favor of the soldier, and usually on the basis of proved tuberculous activity during military service.

Bruns General Hospital.—This hospital was designated a specialty center for tuberculosis in August 1944, with an allocation of 750 beds for tuberculosis. Lt. Col. (later Col.) George J. Kastlin, MC, was chief of Medical Service until December 1945, when he was succeeded by Maj. (later Lt. Col.) George C. Owen, MC, with assistant chiefs in charge of two large sections for tuberculosis. When the directive of August 1944 was issued, 26 wards were set aside for patients with tuberculosis. The relatively small number of physicians on the staff at the time who were well qualified in the treatment of tuberculosis was augmented as rapidly as possible. Capt. (later Maj.) Lawrence H. Kingsbury, MC, was brought in from the surgical service at Fitzsimons General Hospital as chief of thoracic surgery, and the work at the two hospitals was coordinated by mutual visits.

The hospital had a difficult task, however, for the report [57] for 1944 noted that the rate of growth was more rapid than the officer, nurse, and enlisted personnel could properly handle. All services felt the impact of the abrupt designation of the hospital as a specialty center. At the end of the year, 697 tuberculous patients were in the hospital. During 1944, 6,118 X-ray films of the chest were made, out of a total of 13,752 films of all parts of the body. Pulmonary tuberculosis accounted for 17 percent (123 cases) of the discharges for disability. The majority of discharges were to the Veterans' Administration and convoys seriously depleted the force of officers necessary to care for patients.

Since Bruns General Hospital was designated to care for cases of tuberculosis from overseas, the morale problem was exceptionally difficult. The hospital was isolated and filled with patients who had not seen their families for months or years. Unusual measures, which proved notably successful, were projected to meet the problem (pp. 388–390). Education was a principal objective, directed particularly to teach acceptance of continuing care at the hands of the Veterans' Administration after discharge from the hospital.[58]

In 1945, it became necessary to increase the allocation of beds to more than a thousand because of the continuing influx of cases from overseas. The problem was complicated in the second half of the year by the arrival of many

[57] Annual Report, Bruns General Hospital, 1944.

[58] The Care of Tuberculous Patients Pending Discharge From the Army. Bull. U.S. Army M. Dept. No. 74: 44–46, March 1944.

patients with severe disease who had been liberated from Japanese prison camps. Personnel needs were great and, unfortunately, could not be well met, because demobilization of medical officers was under way.

In spite of these difficulties, an excellent professional spirit was maintained. Staff conferences, on the model of those held at Fitzsimons General Hospital and leading civilian hospitals for tuberculosis, were held at regular and frequent intervals, and cases were expertly presented and discussed. A pulmonary function unit was established in order to introduce the latest methods used in the study of respiratory physiology.

Close contact was maintained at all times with the Office of the Surgeon General, which was called upon for more direct assistance than was required by the longer established Fitzsimons General Hospital. The system of supervision, the methods of treatment and disposition, the proportion of cases on collapse therapy, and the system of clinical conferences were similar to those at Fitzsimons General Hospital and civilian hospitals for the care of tuberculous patients.

Moore General Hospital.—The third specialty center for tuberculosis, established in 1945 at Moore General Hospital, was necessary because demobilization of men at separation centers resulted in the discovery of cases of tuberculosis in numbers exceeding the capacity of Fitzsimons and Bruns General Hospitals. The lesions found were usually symptomless and of minimal extent, although occasionally moderately advanced cases were encountered in men who, surprisingly, had been doing full duty and were not aware of any respiratory disease.

Since Moore General Hospital was not staffed or equipped for tuberculosis, it was necessary to bring in new personnel and to specify that patients requiring thoracic surgery were not to be sent there. Army Service Forces Circular No. 456, 29 December 1945, established the center and specified that (1) cases of minimal extent, (2) unilateral cases of moderately advanced tuberculosis appropriate for pneumothorax treatment, (3) cases of suspected tuberculosis requiring prolonged observation for diagnosis, and (4) cases of pleurisy with effusion were to be sent to Moore General Hospital. Cases requiring extensive surgical procedures and cases in which the prognosis was bad were to be referred to other general hospitals or discharged directly to the Veterans' Administration. Tuberculous patients were placed on the medical service, of which Lt. Col. J. Murray Kinsman, MC, was chief when the hospital was designated as a specialty center for tuberculosis.

Cases within the first three categories named were frequently found at separation centers, and the space assigned for tuberculosis at Moore General Hospital filled rapidly. Within a few months, there were more than a thousand patients at the center. Most of these had lesions of minimal character, many of them difficult to establish definitely as tuberculous, being of slight extent and without demonstrable tubercle bacilli. Thus, many patients remained for several months for exhaustive study to establish diagnosis of the

disease itself, and its state of activity. The principles in practice were later summarized in TB MED (War Department Technical Bulletin) 221, dated 29 April 1946, and change 1 thereto, dated 27 December 1946. Moore General Hospital was ultimately (1946) transferred to the Veterans' Administration, obviating physical transfer of patients designated for Veterans' Administration care.

The three general hospitals designated as specialty centers for tuberculosis normally received medical records and X-ray films of cases originating overseas when the patients were transferred to these hospitals. The reports from Bruns General Hospital indicate that the records were of good quality. All three hospitals also made extensive use of induction films of patients obtained from the X-ray file of the Veterans' Administration in Washington, D.C., where they had been stored immediately after induction. These films proved highly useful in evaluating the age of lesions as a guide in treatment and disposition. The experience at Fitzsimons General Hospital indicated that early in the war, when cases were not infrequently overlooked at induction, the patients sent to the hospital were predominantly those in whose induction film a lesion could be seen. In the second half of the war, lesions requiring hospitalization did not, in the majority of cases, appear to represent an extension from a lesion visible in the induction film, but rather a new development during Army service.

ORIENTATION AND REHABILITATION

The problem of rehabilitation of tuberculous patients in Army hospitals could not be met in the same manner as with diseases of short duration or wounds and accidents leaving a mechanical handicap. With these, the reconditioning services of Army hospitals were highly effective during the period of convalescence. As regards tuberculosis, however, it was impractical to retain patients in Army hospitals long enough for arrest of the disease and rehabilitation. AR 615–361, 14 May 1947, required discharge when the diagnosis of active disease and the need for prolonged care were established, although specifically prohibiting transfer as long as the health of the patient would be jeopardized.

In practice, this regulation was interpreted as authorizing that degree and extent of care in an Army hospital necessary to prepare patients for transfer—enlisted men to the Veterans' Administration and officers to their own care—in the best condition to profit by continued hospital treatment. In the three tuberculosis centers of the Army, enlisted men were retained on an average for 4 months. Officers were held longer on the basis of the possibility of their retention for continued service.[59]

Although reconditioning of tuberculous patients in Army hospitals was thus not possible in the same sense as for patients recovering from pneumonia

[59] See footnote 3, p. 331.

or fracture of bones, the need for thorough orientation with respect to the disease was clearly evident. In 1945, on the advice of the Office of the Surgeon General, a department for orientation was established at Bruns General Hospital under the direction of Capt. (later Maj.) Bernard D. Daitz, SnC. Captain Daitz, with an extensive background of civilian experience in rehabilitation of patients with tuberculosis, introduced modern methods of instruction of patients, winning their confidence, and stimulating an improved morale. He prepared TB MED (War Department Technical Bulletin) 222, dated 16 May 1946, while assigned to Bruns General Hospital, which proved a model for other Army hospitals caring for tuberculous patients, and this was later modified to meet the special problems of patients under care of Veterans' Administration hospitals.

The ideal program in the care of tuberculous soldiers embraced a proper integration of medical treatment, social work, vocational counseling, and intelligent use of the patient's leisure time. The immediate and most important objective was to educate patients concerning their need for continuing medical treatment. This involved, first, educational measures on the nature of tuberculosis and, second, measures to overcome the apathy, or even resentment, with which soldiers reacted to provision for their treatment by the Army or other Federal agencies.

To train ward officers and other hospital personnel as teachers, a system of staff indoctrination was devised, which included lectures and discussions on (1) problems of tuberculous patients, (2) pathogenesis and treatment of tuberculosis, (3) psychology of tuberculous patients, (4) problems in nursing, (5) problems in nutrition, (6) occupational therapy, and (7) the best utilization of the Red Cross in the program. A tuberculosis advisory council was established to implement the program of staff indoctrination and teaching of patients. All of the services concerned in the care of patients were represented.

The orientation program for patients was coordinated by an officer from the medical service. Since the great majority of the tuberculous were bed patients, ward officers were made responsible for instruction of patients on the nature of the disease. On arrival at the hospital, each patient was given a copy of "What You Should Know About Tuberculosis," an educational pamphlet published by the National Tuberculosis Association and modified for Army use by the Consultant in Tuberculosis, Office of the Surgeon General. Medical officers with proved special capacity for instruction were sent from ward to ward to discuss medical problems with patients.

Counseling on other than medical problems was made the responsibility of those best qualified in the various fields concerned, including the educational reconditioning services, the personal affairs division, the Red Cross, the librarian, and others. It was important at the outset, and concurrently with the program of medical instruction, to reassure patients as far as possible with regard to the future and to ascertain and develop their educational

and vocational interests and capacities. Since most of the patients would ultimately be beneficiaries of the Veterans' Administration, the system of care at Veterans' Administration hospitals and their rights and privileges as veterans under the Vocational Rehabilitation Act (Public Law 16, 78th Cong.) and the Servicemen's Readjustment Act of 1944 (Public Law 346, 78th Cong.), more commonly known as the G.I. Bill of Rights, were carefully explained. At the same time, patients were asked to discuss freely their personal problems and their complaints. These principally centered on their isolation from friends and relatives. Most of the patients had been overseas for many months, and the long separation from home brought their morale to a low ebb. Everything possible within reason was done to overcome this sense of isolation. The specific complaints most frequently heard were about diet, and these were more concerned with its palatability and serving than with its basic quality. Serious attention was given to these complaints, and noteworthy improvement in dietary service was accomplished.

Motion pictures of both educational and diversional character were presented on a schedule adapted to the strength of the different groups of patients, and extensive use was made of the library. Many patients undertook studies that yielded academic credit. The vocational interests of patients were studied by the Kuder vocational interest test (Kuder Preference Record), and patients were made acquainted with the correspondence courses available through the United States Armed Forces Institute.

Occupational therapy was carried out on a scale commensurate with the patients' strength. The various forms of light occupation used in Army hospitals were employed, and a large majority of patients availed themselves of some form of occupational therapy. Indeed, a major difficulty was to restrain them. Light occupation was often sought by patients whose medical regimen demanded strict bed rest.

Orientation programs on a less formal basis were in effect at the other Army hospitals for the tuberculous. The period of time during which the plan formally established at Bruns General Hospital was in operation was too short to determine how effective it could be. Some good was definitely accomplished. This was substantiated by the information obtained from questionnaires filled out by patients and by their attitude later in veterans' hospitals. Had the need developed for continued hospitalization of tuberculous patients in Army hospitals, it is believed the program as developed at Bruns General Hospital would have proved highly effective.

Part V. Care of Recovered and Captured Prisoners of War

RECOVERED PRISONERS OF WAR

Tuberculosis in recovered prisoners of war has already been discussed in the sections on the individual theaters in this chapter. An increased incidence, as compared with the general rate for troops in the theater, was found

in men who had been prisoners of the German and Japanese military forces for some months. Exact studies of the incidence were not made, because of a number of circumstances arising at the time. In the European theater, the liberation of prisoners in the course of rapid movement of American troops through Germany occurred at a time of grave shortage of X-ray film in the theater. Accordingly, roentgenograms of the chest were not made on all recovered prisoners, as had been the hope of the Office of the Surgeon General, but only on those who were hospitalized for one or another reason. As has been pointed out (pp. 344–345), the incidence of tuberculosis discovered in the hospitalized recovered prisoners in the European theater averaged about 6 men per 1,000, or approximately six to eight times the general average for troops in the theater. However, the group examined by X-ray were selected simply because of malnutrition or evident illness, and it is reasonable to suppose that the incidence of tuberculosis was higher in this group than in recovered prisoners who appeared in good health.

Rates recorded for prisoners recovered in the Pacific area were somewhat higher. Several reports indicated that approximately 1 percent of the men recovered in the Philippines had what was believed to be active tuberculosis. However, prisoners were recovered at such a wide number of points, where facilities for X-ray study were not available, that an overall rate for the Pacific is unobtainable. A board appointed by The Surgeon General, including representatives of several medical specialties, examined 4,618 repatriated prisoners at West Coast debarkation hospitals. Out of 3,742 who were checked with roentgenograms of the chest, 101, or 2.7 percent, showed evidence of active pulmonary tuberculosis.[60] A preliminary examination by Major Roper of films made at Letterman General Hospital on prisoners recovered in the Pacific area brought to light 8 cases of active minimal and 3 cases of active moderately advanced tuberculosis, and 2 cases of pleural effusion. Of this group, only 2 of the minimal and 2 of the moderately advanced cases, and 1 of the cases of pleural effusion, had been reported on admission to the hospital. The total incidence of active cases, assuming that the pleural effusions were tuberculous, was thus 13 in 966 or about 13 per 1,000, a figure much higher than the average incidence in nonprisoner groups at separation. (See chart 19 for incidence at separation in troops with and without foreign service.) Various other individual reports on sample liberated groups, all showed rates much above the average for troops on duty in the Pacific theaters. Hence, there is good reason to believe that a general increase of tuberculosis occurred in prisoners. This was attributed to one or both of two principal reasons: (1) Breakdown of small latent lesions that might otherwise have remained stable, and (2) actual acquisition of new infections as a result of exposure in prison camps. The latter was believed to be much more of a factor in the Pacific area than in the European theater.

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[60] Morgan, H. J., Wright, I. S., and Van Ravenswaay, A. C.: Health of Repatriated Prisoners of War From the Far East. J.A.M.A. 130: 995-999, 13 Apr. 1946.

In the European theater, as a rule, American prisoners were quartered in barracks separate from those used for other prisoners, or were quartered with British prisoners. In either event, there was relatively little opportunity for exposure, as the incidence of tuberculosis was comparatively low in both armies. However, as medical officers in the theater pointed out, and as noted elsewhere in this chapter, frequently prisoners lived in quarters that had been grossly contaminated by previous occupants.[61] The incidence of tuberculosis in Russian and other prisoners of war was very high, and from time to time prisoners from the U.S. Army were housed in quarters that had been previously occupied by Russian and other troops and still contained material that might have been infected, such as bedding, furniture, and kitchen utensils.

In many recovered prisoners of war in whom tuberculosis was discovered, the disease was complicated by malnutrition. Prisoners in both European and Pacific theaters had been on an extremely low caloric diet and in general had suffered great loss in weight. Whether this had a specific effect upon the progress of tuberculosis could not be determined on the basis of exact studies, but a relationship between malnutrition and tuberculosis is generally accepted, and it is logical to assume that impaired nutrition in U.S. troops favored the development and spread of tuberculosis among them.

Not a few of the troops had other diseases, such as dysentery and malaria, and it is reasonable to suppose that resistance to tuberculosis was lowered also to some extent by these concomitant diseases.

Special attention was devoted to prisoners on their return to the United States, as noted elsewhere in this chapter, and a good followup was maintained. In view of the hardships that many of these men endured, and the notorious tendency for tuberculosis to make its appearance years after the acquisition of infection, it was considered advisable that these men be followed as a special group in the Veterans' Administration for years to come.

CAPTURED PRISONERS OF WAR

The medical treatment of captured German and Japanese soldiers who were found to be afflicted with tuberculosis was a part of the general program of hospital care in each theater. As prisoners were taken, they were transferred to appropriate hospitals in the communications zone, which were usually of station hospital type. When the number of patients became sufficiently large, entire hospitals were reserved for sick prisoners of war. Each of the hospitals devoted to the care of sick and wounded enemy prisoners had some patients with tuberculosis. As the number increased, it was found advantageous to designate certain hospitals with suitable medical personnel for concentration of patients with tuberculosis. The same practice, it may be stated, was followed by the Germans.

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[61] See footnote 17, p. 340.

Insofar as possible, hospitals designated for the care of sick and injured prisoners of war were staffed by captured members of the Italian, German, or Japanese medical departments. Certain hospitals moved forward with the advancing army, so that the transportation problem in taking care of sick prisoners was minimized. For example, the 7029th Station Hospital, which was in the neighborhood of Pisa in the last weeks of the war and housed a good many tuberculous Italians, had been designated for the care of prisoners of war many months previously in North Africa. The 334th Station Hospital (German staffed), near Florence, served an adjoining stockade for German prisoners and contained a few patients with tuberculosis. A group of hospitals near Isigny in Normandy were combined to form a hospital center for prisoners of war; one of these, the 8274th General Hospital (Provisional), Calvados, France, was designated to house a considerable number of captured Germans proved to have tuberculosis. Certain hospitals in England, particularly those that had been previously well staffed with officers experienced in tuberculosis, including the 304th Station Hospital near Henley-on-Thames and the 327th General Hospital near Blockley, were designated as centers to which German patients with tuberculosis could be sent.

The general principle followed was that prisoners with tuberculosis should be sent to those hospitals where German doctors with particular experience in the disease were members of the staff. A wide variation was found in the caliber of the men concerned, but in general it was good. Diagnosis by radiological and laboratory methods was excellent in certain of the hospitals just named, and care was superior within the limitations of equipment available. The discipline among patients was especially noteworthy. The same amenability to discipline in German prisoners was noted when they were treated for tuberculosis in the United States. Pneumothorax was practiced expertly by German physicians, many of whom were graduates of medical classes after 1935.

After the termination of hostilities, as conditions became more stabilized for medical care in Germany, patients with tuberculosis were transferred to hospitals within the American occupied zone in Germany.

Treatment in the United States

Cases of tuberculosis were discovered in all groups of prisoners in the United States, and care entirely comparable to that given American patients with tuberculosis was accorded them. Special provision was made for tuberculous prisoners of war by War Department Prisoner of War Circular No. 11, 8 February 1944, which directed that those afflicted with pulmonary tuberculosis be sent to the prisoner-of-war camp station hospital in Florence, Ariz. At this hospital, they were to be examined by a mixed medical commission of representatives from neutral countries with a view to repatriation. It was directed that cases of nonpulmonary tuberculosis be sent for care to certain

general hospitals designated in each service command for the care of prisoners of war. Subsequently, when the station hospital at Florence was abandoned as a center for such patients, about 50 tuberculous German and Italian prisoners of war were sent to Fitzsimons General Hospital, where a number had already been sent from other places pending final determination of policies governing the treatment and disposition of sick prisoners of war. On 5 January 1945, a telegram from the Office of the Provost Marshal General to several service command headquarters directed that, pending further revision of policy, prisoner-of-war patients with pulmonary tuberculosis should be transferred as follows: German prisoners to Glennan General Hospital, Okmulgee, Okla., Italian prisoners to Bruns General Hospital, and Japanese prisoners to the prisoner-of-war camp station hospital, Camp McCoy, Wis. Wherever German prisoners of war were concentrated, a sharp difference of opinion was found to exist in the Nazi and anti-Nazi groups, and it was generally necessary to house them in entirely separate wards.

Relatively large numbers of Italians were found to have tuberculosis. The German Army appeared to have been screened in a much more thorough manner than the Italian. In fact, the number of tuberculous Italians was so high in certain areas that it was considered advisable by Army Service Forces Circular No. 342, 14 October 1944, to make mass X-ray surveys of all Italian service troops for the discovery of cases of tuberculosis.

The total number of Japanese prisoners in the United States was relatively small, and therefore the problem of tuberculosis in Japanese prisoners was minor. A small number were kept for care at the station hospital of Camp McCoy. No significant differences were noted in the character of tuberculosis in the different groups, but the experience at Fitzsimons General Hospital indicated that the German prisoners, as a rule, made better progress than Italian, a fact attributed to their better discipline and acceptance of medical direction.

A comprehensive report on the medical care of prisoners of war in a general hospital in the United States was made by Col. Louis B. LaPlace, MC, at Glennan General Hospital.[62] Glennan General Hospital was in close proximity to a number of large prisoner camps and was well adapted to care for prisoners. Ninety percent of the patients were Germans and Austrians, and the remainder were nationals of Axis satellite or invaded countries. It functioned as an installation specifically for prisoners of war from August 1944 to May 1945. Glennan General Hospital was ultimately converted to a general hospital for American personnel, and all of its prisoner patients were transferred to Prisoner-of-War General Hospital No. 2, established at Camp Forrest, Tenn., which had the great advantage of a large barracks area where patients unfit for duty, but not requiring hospital care, could be accommodated.

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[62] LaPlace, L. B.: Tuberculosis at a Prisoner of War Hospital. Bull. U.S. Army M. Dept. 7: 398–399, April 1947.

To the greatest extent possible, Glennan General Hospital and Prisoner-of-War General Hospital No. 2 were staffed with German medical department personnel, including medical officers and enlisted men. The professional aptitude of the German medical officers varied considerably. A number with excellent qualifications were on duty, but as among the patients, there was a definite difference in attitude among them, based on adherence or opposition to the Nazi party.

The staff of the medical service at Glennan General Hospital was composed of two Americans and eight German medical officers. The number of German ward attendants averaged 50 for the 11 wards utilized by the medical service. Only one American enlisted man was needed to supervise the entire medical service. American nurses were not utilized on the wards.

Approximately 31 percent of the German patients at Glennan General Hospital had tuberculosis of the respiratory tract. This relatively high incidence was due to the fact that Glennan was the only hospital for prisoners of war designated for the specialized care of tuberculosis. As Colonel LaPlace pointed out, the tuberculosis section constituted a special problem. It admitted 304 patients in whom the diagnosis of tuberculosis of the lung or pleura was established. Because of anticipated repatriation, active cases could receive only conservative treatment, including pneumothorax. Since repatriation was slow, these patients accumulated in the hospital until they filled 6 of the 11 medical wards. In spite of the severity of a large percentage of the cases, only five deaths occurred on the tuberculosis section; of these, three patients were prisoners of Russian origin who had accepted service in the German Army. The clinical course of the disease, in the majority of instances, was relatively benign.

Special diets were available to patients who needed them. All patients on the tuberculosis section at Glennan General Hospital, according to Colonel LaPlace, received a routine diet of 2,500 calories daily, with vitamin supplements. Colonel LaPlace's report pointed out that Glennan General Hospital was a noteworthy example of this country's full adherence to the terms of the Geneva Convention. Prisoners of war were hospitalized in one of the best constructed and equipped of any except permanent Army hospitals.

The number of tuberculous patients admitted to the medical service constituted 2.6 percent of all admissions to the hospital. Among the 10 percent of patients in the tuberculosis section who were not Germans or Austrians were Russians, Poles, Czechs, French, Yugoslavs, Arabs, and others. Most of these had been persuaded to join the Wehrmacht or Arbeitsdienst by a period of starvation and exposure in a concentration camp. In many cases, it is believed that mistreatment had caused activation of tuberculosis.

In this connection, it may be noted that the admission rate for tuberculosis in German prisoners of war, as recorded in the Medical Statistics Division of the Office of the Surgeon General, was 1.9 per 1,000 per annum in

1944. This, for the most part, represented admission because of symptoms. Occasionally, groups were surveyed more specifically for tuberculosis; such surveys increased the rate. An unusually high rate was observed in one conducted in the First Service Command. The combined figure for active and inactive tuberculosis of reinfection type and chronic fibrotic tuberculosis found in this survey was 55 cases in 4,041 examinations.

The tuberculosis section at Glennan General Hospital was a subdivision of the medical service and was accommodated in seven standard wards. One of these, a so-called international ward, was designated for the Russians, Poles, and anti-Nazi Germans who required protective segregation from the other Germans in the hospital.

The tuberculosis section was supervised by an American chief and assistant chief of the medical service and one sergeant. The international ward was administered directly by American medical officers. Otherwise, all medical officers in attendance were members of the German Sanitätsdienst who were classified by the Geneva Convention as protected personnel rather than as prisoners of war. The German chief of section was a relatively well qualified specialist in tuberculosis who, prior to capture, had served in a submarine and at an outpost on the Arctic Circle.

Certification of patients for repatriation was an important part of the work and caused many difficulties. According to the Geneva Convention, all prisoners of war who had active pulmonary tuberculosis, as indicated by the finding of acidfast bacilli, were to be returned to Germany as soon as possible. As a result, patients attempted to substitute a known positive sputum for their own. According to Colonel LaPlace, the German-protected personnel were accused of being collaborationists if they did not help in this subterfuge. Sputum reports were therefore considered unreliable, and the activity of tuberculosis was often almost impossible to determine.

Treatment included principally rest, a high caloric diet with vitamin supplements, and pneumothorax as indicated. Radical surgical therapy was not undertaken because of the prospect of repatriation for definitive care. Many patients became arrested cases in the hospital and were returned to light duty.

Of the 304 cases of tuberculosis, 267 were pulmonary and 37 had tuberculous pleurisy with effusion. In 14 cases, both pulmonary involvement and pleural effusion were present. Extrapulmonary cases included tuberculosis of the larynx, epididymis, joints, kidney, meninges, peritoneum, and cervical lymph nodes. In all, there were 14 nonpulmonary cases.

The experience of Glennan General Hospital has been recorded in detail, because of the comprehensive character of the report on tuberculosis at that hospital. The problems and care as outlined may be considered as representative of the service at the other hospitals for prisoners of war in this country.

TREATMENT UNDER THE MILITARY GOVERNMENT IN GERMANY

The control of tuberculosis formed an important part of the public health program of the office of military government in each of the occupation zones. It was accentuated in Germany by the total disruption of tuberculosis services following the collapse of the Nazi government. Prior to World War II, Germany had a well-organized program, which was rapidly diminishing the prevalence of tuberculosis in the Reich. Following the First World War, German public health experts had adopted a program based on improved dispensary facilities for discovering cases of tuberculosis, better care in homes and sanatoriums, increase in facilities for treatment, and centralization of finance in general measures for control. At the outset of the Second World War, case-finding surveys with roentgenograms were progressing on a huge scale, but after the middle of 1943 the intense bombing of German cities destroyed so many facilities that the X-ray program came almost to a standstill.

The breakdown in the general public health program had resulted in admitting to industry a good many workers with tuberculosis who, in prewar times, would not have been accepted for work. It is generally believed that this breakdown in service resulted in the spread of tuberculosis within the German population. The admission of tuberculous persons to industry was rationalized by the Nazi officers for tuberculosis control by official communications stating that the danger of transmission of tuberculosis had been exaggerated in the past.[63]

In addition, during the war, large numbers of laborers were imported from adjoining countries with little or no screening for tuberculosis. It is probable that many cases of communicable tuberculous disease were admitted in this way, for the general tuberculosis rates in surrounding countries were much higher than in Germany.

When the U.S. Army took over the public health program for the American Zone, the control of tuberculosis was proceeding on a purely local basis. Central control, previously located in Berlin, was no longer in operation and, in fact, many of the former leaders of the program, having been prominent adherents of the Nazi party, were under detention in Army headquarters.

The local unit of tuberculosis control, the Fürsorgestelle, was in operation in most communities, ostensibly in the same manner as before the war. However, qualified personnel was much reduced in number, and many of the German clinics had been forced by bombing to leave their regularly constituted quarters and to take up operation in inferior dwellings, often with inadequate equipment. Moreover, the visiting by Fürsorgestellerinnen to the homes of tuberculous patients had been almost discontinued because of the

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63 Dr. Kayser-Petersen, General Secretary: Arbeitseinsatz von Tuberkulösen, Bericht über das Geschäfts Jahr 1940–1941, Reichs-Tuberkulose-Ausschuss, Berlin. [Captured German document.]

lack of transportation. No motor cars were available, as a rule, and in the rare circumstances where motor transportation could be obtained, gasoline was very short, so that few visits could be made. At the same time, facilities for reporting tuberculosis were much reduced, so that no clear picture of the prevalence of tuberculosis was obtainable in most localities.

In September 1945, a tuberculosis section was organized in the Preventive Medicine Branch of the Public Health Branch of Military Government for Germany (United States) in Frankfurt and Berlin. Preliminary surveys were made by Capt. S. C. Stein, MC, and the office was taken over by the Consultant in Tuberculosis from the Office of the Surgeon General on a temporary duty basis on 1 September 1945. Every effort was made in the succeeding months to promote restoration of the German program to its prewar condition. Insofar as personnel qualifying under the denazification rules were obtainable, suitable public health officers, experienced in tuberculosis control, were appointed in the Länder, Kreisen, and smaller units. In November 1945, the section was taken over by Lt. Col. Leo V. Schneider, MC, who, in addition, acted as aide to the chief of the public health branch. Under his direction, great progress was made in improving reporting and in the provision of beds for tuberculous patients throughout the U.S. Zone. Subsequently, Lt. Col. Gilberto S. Pesquera, MC, was appointed tuberculosis consultant for the Office of Military Government. In a series of reports to the Director of the Public Health Office of Military Government in May 1946, further progress was indicated, including better utilization of beds—particularly with respect to the distribution of beds for German civilians and displaced persons—and the control of dissemination of disease from open cases.

In each major division of the occupied zone, an American medical officer in the office of the chief of the local public health branch was assigned the specific task of stimulating the program for control of tuberculosis. Forms were prepared for proper reporting, and constant effort was made to increase the number of beds available for care of tuberculous patients discovered in the German population.

The 9 October 1945 memorandum of the Consultant in Tuberculosis, Office of the Surgeon General, called attention to the progress effected in the transfer of tuberculous German prisoners of war from Army hospitals to German hospitals and sanatoriums for civilians and to the measures followed in handling tuberculosis among displaced persons. The latter proved a large and difficult problem, which was jointly attacked by the army of occupation (Third, Seventh, and Ninth U.S. Armies), the Office of Military Government, and the United Nations Relief and Rehabilitation Administration, the chief public health officer of which was supplied by the U.S. Public Health Service. This report outlined in detail the responsibilities and shortcomings of the German civilian public health organization for tuberculosis control at and below the Land level. It laid special stress on the inadequacy of reporting, the insufficiency of clinics and of hospital and sanatorium beds

for tuberculosis, the number of open cases in homes, the serious housing problem and resultant crowding, and the impaired nutrition of the population. It was pointed out that in a typical city of about 140,000 (Augsburg, Germany, was cited as the example) more than 2,000 persons with open tuberculosis were believed to be resident in homes, rather than in sanatoriums. The housing shortage in the American Zone was such that the number of occupants per room in the large cities had more than doubled as compared with the prewar figure. The official food ration at the time provided only 1,300 calories a day, and although this was supplemented by 300 calories of nonrationed foods by many persons with access to rural areas around cities, at best the diet fell far short of that believed essential to maintain normal resistance to disease.

The mortality from tuberculosis was far greater in Berlin than in other parts of the American Zone. Recorded annual rates for Berlin regularly exceeded 200 per 100,000 population, whereas the rates reported in other parts of the zone occupied by American troops seldom exceeded 70. It is believed, however, that in the majority of instances the records were inaccurate and incomplete. Before the end of the year, a reasonably good program was in effect, the future of which depended upon the full organization of the general public health program in Germany.

In the report last cited, in addition to recommendations for American supervision of German medical organization and the continued effort to increase facilities and personnel for the care of tuberculosis in the U.S. Zone, the need for some central German civilian advisory service was indicated. This recommendation was entirely in line with general policies being developed not only in the public health field but also in the realm of economics and civil government. Unfortunately, German civilians of the required caliber were not available. The former General Secretary of the Reichs-Tuberkulose-Ausschuss was living in the zone but was not eligible under the regulations prevailing with respect to persons with previous Nazi affiliations, nor was it possible during the period covered by this history to find anyone with comparable qualifications who was eligible.

At the end of 1945, it appeared likely that a rise in the tuberculosis rate would ensue, as it did after World War I, but it was believed that improvement in the local organizations, supplemented by assistance from a partially unified Germany, if this were ultimately effected, would stem this in time.

Part VI. Tuberculosis in British and Canadian Military Forces

Published accounts offering valuable material for comparison with the experience of the U.S. Army are available from the Royal Navy, the Royal Air Force, and the Canadian Army.

ROYAL NAVY

The military forces in Great Britain required a physical examination but not an X-ray examination prior to induction into service. A substantial fraction of the Royal Navy,[64] however, was examined by 35-mm. fluorography after varying periods of service, and many of those so examined were re-examined 1 to 2 years later. The following summary of the first examination was made by the Consulting Physician in Diseases of the Chest to the Royal Navy, who was in responsible charge of the examinations:[65]

> Fluorography of 479,373 apparently healthy male personnel of the Royal Navy showed that 6,077 (12.7 per 1,000) had radiological signs of adult-type pulmonary tuberculosis. In 47.9 percent of these the lesion was "minimal."
>
> Of 23,344 WRNS, 213 (9.1 per 1,000) had similar evidence of tuberculosis, and the lesion was minimal in 55.4 percent of these.
>
> Similar investigations among civilians will no doubt bring to light large numbers of cases of pulmonary tuberculosis of this slight degree, raising difficult problems of disposal and treatment.
>
> In some of these minimal cases the disease is arrested, or is retrogressive, but in others it is progressive. Careful study is needed to decide whether the infection is active, and investigation in hospital is essential. When 2,911 sailors with minimal lesions were first studied in hospital 16 percent showed evidence of active infection, while in 63 percent the disease appeared to be inactive but the stability of the lesions was doubtful. In 21 percent the disease was arrested.
>
> Naval personnel with apparently inactive minimal tuberculosis have been placed on light shore duties and kept under observation. Study of these cases shows that the younger the patient the more likely is the disease to become active, and the relapse to be serious.

A significant finding, quite comparable to the results in induction stations in the United States, was a rise in the diagnosis of tuberculosis with advancing age in both males and females. In the four decades from 10 to 50 years of age the rate per 1,000 for males was 8.8, 10.7, 19.7 and 32.8, and for females 6.9, 9.1, 14.9, and 12.7. (The number of females in the 40- to 49-year period was too small to make the figure fully valid.)

An equally significant feature of the examination was the number of cases discovered in the minimal stage, the percentage being much higher than that discovered by the conventional methods of physical examination.

This is in accord with general experience in mass radiography. It is of interest to note that the percentage of all tuberculous cases discovered in the minimal stage did not vary significantly in the different age periods. Followup studies indicated clearly that the younger the patient with radiological evidence of minimal tuberculosis, the greater the likelihood of its displaying activity.

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[64] History of the Second World War, United Kingdom Medical Services. Medicine and Pathology. London: Her Majesty's Stationery Office, 1952, pp. 319–332.

[65] Brooks, W. D. W.: Management of Minimal Pulmonary Tuberculosis Disclosed by Fluorography. Lancet 1: 745–748, 10 June 1944.

The average for the whole force examined was 12.7 per 1,000 for men, and 9.1 for women, figures slightly greater than those for rejections for pulmonary tuberculosis at induction stations in the United States.

A later summary of the experience of the Royal Navy [66] threw further light on the relation of age to prognosis. Naval personnel with apparently inactive tuberculosis were placed on light shore duty and kept under observation. Almost all of those whose lesions proved active with the passage of time were under 25 years of age.

This last summary discloses that by the end of 1944, 91,959 ratings passed as normal on a first fluorographic examination were reexamined, and 479 cases with radiological evidence of tuberculosis were discovered. Comparison with the original film showed that in 123 the lesion was previously existent but missed. This yields a figure of 1.3 per 1,000 of those fluorographed, which agrees very closely with the estimate of 1.0 to 1.5 cases per 1,000 of significant tuberculosis missed at induction in the United States, as calculated by Long and Stearns from a rereading of 53,400 induction films. In both groups, the reasons for failure of detection and recording were the small size of the lesion, presence of the lesion behind skeletal structures that cast a denser shadow, proximity to the dense hilus structures, and, in some cases apparently, clerical error.

Of the 479 cases found on reexamination, however, the great majority showed no evidence of disease in the initial film. These must have represented new infections or manifestations of endogenous spread from an unknown focus elsewhere. It was significant that of the new group 73 percent were found in the minimal stage, a figure contrasting sharply with that of 48 percent found for minimal tuberculosis on initial fluorography. Further analysis showed that the total amount of new tuberculosis discovered on the second examination increased with the length of lapsed time since the first fluorography. In men who had their second examination within a year or less, the rate was 2.4 per 1,000; in those reexamined only after an interval of 3 years, the rate was 7.3. The average for all groups was 3.4. In about one-third of the cases, there was definite evidence of activity.

In studying these figures, it is of interest to note that an appreciable number of cases of tuberculosis developed in the course of time also in United States and Canadian troops who had been screened before acceptance and that this increase was greater in those who had had military experience overseas than in those who had not;[67] also, that the annual mortality from tuberculosis in the Army and in the ex-Army population rose steadily during the war years.[68]

[66] Some Problems of Fluorography. Roy. Nav. Med. Bull. No. 20: 1–9, 1945.

[67] See footnote 13, p. 337.

[68] (1) Adamson, J. D., Warner, W. P., Keevil, R. F., and Beamish, R. E.: Tuberculosis in the Canadian Army, 1939 to 1944. Canad. M.A.J. 52: 123–127, February 1945. (2) See footnote 41, p. 372.

The analysis published by the Royal Navy of the invasions by disease and deaths of ratings from 1934 to 1944 indicated that approximately 2.5 men per 1,000 were invalided each year for tuberculosis from 1941 on. The rate for officers was somewhat lower. This figure is several times the discharge rate for tuberculosis in the U.S. Army, in which the relatively low rate is explained by the radiological screening carried out prior to induction.

In this place, it is not out of order to point out that the British were at all times less conscious of the problem of compensation than the Americans. Whether tuberculosis was discovered before induction or after was a vital matter in the United States and Canada. The disposition of cases discovered in both categories was approximately the same in Great Britain, but the financial issue was of less concern.

The death rate for tuberculosis in Royal Navy personnel dropped after 1942, following several years at a constant level. It was the hope of the officers concerned that this was the forerunner of the benefits to be expected in the future from mass radiography in the service and discovery of cases in an early and favorable stage.

ROYAL AIR FORCE

The Royal Air Force also made extensive use of 35-mm. fluorography. A report on 190,076 males and 59,951 females was made by Air Commodore R. R. Trail and associates in 1944.[69] All of the subjects of the survey were already in service, and all had been accepted for service on the basis of physical examination. The men had been physically examined 3 to 12 months previously, some very strictly because of their special duties, and the women, all members of the WAAF, 6 months previously on the average. The great majority of each group was under 30 years of age.

The total incidence of tuberculosis was 7.7 per 1,000 in men, the difference, in comparison with the 12.7 discovered in the Royal Navy, being in part attributable to the younger age of the Air Force personnel. In women, the incidence was 9.4; that is, approximately the same as the rate of 9.1 discovered in women in the Royal Navy. Followup examination indicated that the incidence of active tuberculosis was 2.8 per 1,000 in men and 3.6 in women. In men, the figures with respect to age differed from those of the Royal Navy in that active disease was not discovered preponderantly in the youngest age groups, but in increasing extent in the groups up to 40 to 44 years. In women, the peak in the incidence of active disease was in the 20- to 24-year period.

An interesting finding common to the experience of both the Royal Navy and Royal Air Force was the rise with advancing years in the incidence of calcified lesions interpreted as the residua of healed tuberculosis of childhood

[69] Trail, R. R., and others: Mass Miniature Radiography in the Royal Air Force: Report on 250,027 Consecutive Examinations of R.A.F. and W.A.A.F. Personnel. Brit. J. Tuberc. 38: 116-140, October 1944.

type. This rise could signify that childhood-type tuberculosis was much commoner years ago than now, or that the type of lesion terminating in calcification occurred in later years, so that a cumulative rise occurred in the number of healed residua.

As in the U.S. Army, a higher increase in incidence was observed in recovered prisoners of war who had spent many months in prison camps in Germany. A survey of 7,146 recovered Royal Air Force personnel in April and May 1935 showed an incidence of active pulmonary tuberculosis about twice as great as that found in Royal Air Force personnel who had not been prisoners.[70]

CANADIAN ARMY

The control of tuberculosis in the Canadian Army was remarkably effective, and the scientific study to which data on tuberculosis were subjected proved illuminating in the general understanding of the pathogenesis of tuberculosis.

X-ray examination was a requirement on induction in the Canadian Army. As in the U.S. Army, some troops were not examined by X-ray in the early months of mobilization. Subsequently, roentgenograms were made of the chests of men who had been inducted without a film, and those found to have significant lesions were discharged. Approximately a million and a half persons, equivalent to a quarter of the male population and half of all persons of Army age were examined by X-ray in the induction examinations.[71] The incidence of lesions discovered was about 1 percent; a third of the cases discovered, about 5,000, were considered clinically significant and reported to the civil authorities. This byproduct of the war was of notable value to the general program of tuberculosis control in Canada.

A feature of great importance, rendering the results of exceptional value for understanding the hazards of tuberculosis in military service, lay in the sharp distinction maintained by the Canadian military organization between the Army in Canada and the Army overseas. In both, the prevalence was very low by civilian standards, as would be expected in a group well screened by roentgenographic examination. The distinction lay in the fact that the Army in Canada was subjected to a hazard of exposure no greater than that in the civilian population of the provinces, while the Army overseas was exposed to contagion in countries in all of which the death rate, and presumably opportunity for contact with open cases, was much greater than in Canada. For the years 1939–44, the average incidence of tuberculosis discovered in troops in the Army in Canada was 24 per 100,000 per annum, while in troops overseas it was 40. These rates were estimated, respectively, as 15 and 25 percent of the rates in the civilian population in Canada. The

[70] Personal communication, Air Commodore R. R. Trail to author.

[71] Adamson, J. D., and Kecvil, R. F.: Tuberculosis in the Canadian Army. J. Canad. M. Serv. 1: 404–411, July 1944.

rates in each group increased with length of service, ranging, however, from 9 per 100,000 for home troops and 35 for oversea troops in 1941 to 40 and 60 per 100,000, respectively, in 1944.

An even greater difference between troops at home and those overseas was evident in the incidence of tuberculous pleurisy with effusion. In 1941, the rate for the Army in Canada was 30 per 100,000 and that for the Army overseas was 20. In marked contrast, the rates for 1944 were, respectively, 23 and 75 per 100,000.

The increase in the tuberculosis rate with length of service in both groups was attributed, in part, to the foreseeable development with the lapse of time. The excessive increase overseas, however, was explained on another basis; namely, the excessive exposure to tuberculosis in countries with a much greater prevalence of the disease than Canada.

The figures for pleurisy with effusion were believed particularly significant in the latter respect. Analysis of the figures according to the native province of the men who became ill showed that the highest percentage of new cases developed in men from Ontario and the western provinces, where the incidence of infection, as already known from civilian surveys, was low. It seemed logical to believe, therefore, that the high rate of effusion in troops overseas represented the acquisition of primary exogenous infection, a frequent early manifestation of which is pleurisy with effusion. In reaching this conclusion, the Canadian medical officers made allowance for the fact that some of the pleurisy with effusion, diagnosed as tuberculous, might have been due to acute, transient respiratory infections. It was in fact noted that a rise in wet pleurisy occurred in every epidemic of acute respiratory disease. However, after due allowance was made for the discrepancy between home troops and those overseas, the similar trend in cases of pulmonary infiltration and pleurisy with effusion lent strong weight to the view that the latter represented exogenous tuberculous infection overseas. Adamson and his coworkers believed the phenomenon "the natural epidemiological results of a tuberculin-negative group coming into contact with a tuberculous environment."

Canadian authorities carried the lesson into practice by specifying in two directives (14 November and 21 August 1944) that more strict attention be given to a history of pleural pain and to the examination of soldiers with known contact with tuberculosis.[72]

The second directive, and a subsequent note appended to it, indicated that about 4.3 percent of all medical discharges from the Army had been for tuberculosis and that approximately 2.9 percent of medical repatriations were for this disease, of which 1.9 percent (or about two-thirds) were for pleurisy with effusion.

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[72] (1) AGO Directive, 14 Nov. 1944, to departmental commanders. (2) DMS Order 286, 21 Aug. 1944.

These figures for the Canadian Army are of unusual interest. It is unfortunate for the study of epidemiology that in statistics for the U.S. Army, in the Zone of Interior and overseas, a comparable easy separation of troops on the basis of origin cannot be made. Whereas in Canada a large share of the home Army was from the eastern provinces and remained in Canada, in the United States the home Army was constantly a transient force in training for oversea service, and the Army overseas had proportional representation from all parts of the country. Subsequent analysis on the basis of geographic origin may be possible. In the meantime, it appears significant that an unusually high rate of pleurisy with effusion, presumed to be tuberculous, occurred in young U.S. Air Force troops in Italy (pp. 353–357).

Part VII. Significance of Army Experience for Control of Tuberculosis

For many years prior to World War II, tuberculosis mortality in the United States had been declining. The reduction in mortality continued during the war, but at a somewhat lowered rate. Among the reasons for the slowing in the curve of decline were shortages in personnel for civilian public health and hospital practice, increased tempo of work, with corresponding general strain, and absence from the country of a large number of men of an age period with a low general death rate, who were removed from the population on which mortality rates were calculated.

Counterforces were in effect, however, which offset these factors. Although the intensity of labor was increased, wages were far higher than before the war, and although prices were elevated also, the general result was a rise in the standard of living in segments of the population in which mortality from tuberculosis is usually high.

During the war, also, in spite of personnel shortages for public health work, a notable advance in machinery for tuberculosis control took place in the establishment, for the first time, of a Tuberculosis Control Division in the U.S. Public Health Service. This was organized by congressional action in the Bureau of State Services of the U.S. Public Health Service in July 1944. Funds became available shortly thereafter to supplement measures for combating tuberculosis through grants-in-aid to States, enabling the latter to expand their programs in clinics, case finding, and hospitalization.

The examinations at induction stations, as indicated in detail elsewhere in this chapter, brought to light thousands of cases of previously undiscovered tuberculosis. A substantial number of these were placed under treatment immediately. In addition to the saving and prolongation of life thus effected, there resulted a reduction in community exposure to tuberculosis, with presumably a corresponding decrease in development of new cases. The accomplishment in this respect was far from maximum, as reporting of cases was not complete, and followup programs to insure hospitalization of open cases

discovered were not well developed in many parts of the country. In large communities, with well-organized public health programs, followup was good, but in other regions little or none was attempted. Although not specifically mentioned in AR (Army Regulations) 40–1080, dated 31 December 1934 and 10 December 1943, tuberculosis was considered a communicable disease to which the reporting requirement applied. Because of a recognized laxity in reporting cases of tuberculosis, a reminder (specifically mentioning tuberculosis) as to the reporting requirement in AR 40–1080 was issued on 24 July 1944 in War Department Circular No. 313. In some cities, however, by special arrangements between health departments and induction stations, direct report was made immediately, without waiting for report through the normal channels of the State selective service organizations, and State health departments. In New York City, for example, a representative of the Bureau of Tuberculosis of the Department of Health visited the large New York City induction station every night and received direct report on cases of tuberculosis discovered during the day.

The system of hospitalization for tuberculosis in the Army and the normal discharge of patients to Veterans' Administration hospitals for further care, resulted in the treatment of thousands of cases and in corresponding reduction in opportunity to spread the disease to others. Army hospitals and Veterans' hospitals were required by their respective regulations to report cases to State health departments. Special check, however, indicated that reporting was not complete. With changes in personnel, which occurred constantly in Army hospitals, required procedures were not always continuous. To make up in part for deficiencies in reporting, the Consultant in Tuberculosis, Office of the Surgeon General, established a direct relationship in 1944 with the newly established Tuberculosis Control Division of the U.S. Public Health Service, so that all discharges for tuberculosis were reported by States of origin of the men concerned. The Tuberculosis Control Division, in turn, forwarded these reports to individual State health departments. With all the imperfections in the reporting measures, and the lack of suitable followup programs in many States, and in spite of the many tuberculous veterans who refused sanatorium care in the months immediately succeeding discharge, steadily increasing control from the point of view of public health resulted, which should be reflected in a decline of tuberculosis mortality in the future.

In evaluating the effect of the Army's control program on the general antituberculosis campaign, the educational efforts of Medical Corps officers should not be overlooked. In addition to direct counsel given patients with tuberculosis or suspected tuberculosis, they were provided with literature from the National Tuberculosis Association and its affiliates, and hospital patients in general saw motion pictures on the diagnosis, care, and aftercare of tuberculosis. Probably a still greater educational effect resulted from the vast amount of roentgenographic study of the chest done in the Army. X-ray

examination at induction and separation, and the huge number of chest examinations by X-ray in dispensaries and hospitals, made millions of young men and women aware of the danger of tuberculosis and the special measures available to combat it.

On the whole, the tuberculosis control program of the Army was well integrated with the public health program of the country and may be expected to be of continuing favorable influence in the reduction of tuberculosis in the population in postwar years.

CHAPTER XII

Diagnosis and Treatment of the Venereal Diseases

Paul Padget, M.D.

HISTORICAL NOTE

The history of the treatment of the venereal diseases in World War II may well begin on 7 June 1940.[1] The development and application of the methods of treatment used in the U.S. Army prior to this time have been admirably traced and summarized by Siler,[2] and need not be recapitulated.

On 7 June 1940, a meeting of the National Research Council was held in Washington, D.C., to form a subcommittee[3] on venereal disease control. The Subcommittee on Venereal Diseases by its terms of reference was charged with making general recommendations to The Surgeons General of the Army and the Navy concerning the prevention and treatment of the venereal diseases and with acting in a consultative capacity on questions in its special field that might originate from the armed services.

Following this, meetings were held at frequent intervals (six between 7 June and 19 July 1940), and on the latter date, detailed recommendations were approved concerning the diagnosis and treatment of each of the commonly recognized venereal diseases. These recommendations were submitted to the parent committee and eventually were transmitted to the respective surgeons general as the official recommendations of the National Research Council. They were subsequently incorporated in Circular Letter No. 18, Office of the Surgeon General, 10 March 1941, which became the first official statement of a policy for the treatment of these infections to come from the Office of the Surgeon General during the period of the emergency which culminated in World War II. Much later, Circular Letter No. 195, Office of the Surgeon General, 1 December 1943, ordered that the treatment of all patients

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[1] The author is indebted to Dr. Thomas H. Sternberg and Dr. Ernest B. Howard for material on care and treatment which has been incorporated in this chapter. Acknowledgment is also made of the invaluable assistance gained from the use of the private files of Dr. Joseph Earle Moore, formerly Chairman, Subcommittee on Venereal Diseases, National Research Council.

The final editing of this chapter was completed after the death of Dr. Padget.

[2] Siler, J. F.: The Prevention and Control of Venereal Diseases in the Army of the United States of America. Army M. Bull. No. 67, May 1943.

[3] The subcommittee was composed of Dr. Joseph E. Moore, chairman, and Drs. Edwin P. Alyea, Walter Clarke, Oscar F. Cox, John F. Mahoney, and John H. Stokes, members. With the exception of Dr. Alyea, who withdrew after the 14th meeting on 11 March 1942, the members served throughout the wartime period. Dr. Perrin H. Long (later Colonel, MC, USAR) served from time to time ex officio in his capacity as chairman of the Committee on Chemotherapeutics and Other Agents, National Research Council, and as problems dealt with grew in complexity, other specialists were invited to join the subcommittee either temporarily or as permanent members.

hospitalized for venereal disease be on the medical service or under the direction of the chief of the medical service unless there were cogent local reasons to the contrary. Distinction was thus made early between the prevention and control of venereal diseases and treatment of the infected soldier. In the field, it was sometimes the practice to separate these functions entirely and, as in the European Theater of Operations, U.S. Army, to have control and preventive measures administered by the Preventive Medicine Division, Office of the Chief Surgeon, while treatment was supervised by the appropriate consultant of the Professional Services Division, Office of the Chief Surgeon. In the Office of the Surgeon General, both preventive and therapeutic measures were eventually supervised from one office under the Preventive Medicine Service, with free exchange of consultation with the Professional Service and without losing sight of the fact that the individuals in charge of these activities were dealing with separate problems.

It is in keeping with this medical philosophy that a section on the treatment of the venereal diseases appears here. It should be noted that although, to a large extent, the venereal diseases may be grouped for preventive measures and although the two most important (gonorrhea and syphilis) at the end of the war responded to the same antibiotic (penicillin), nevertheless the several venereal diseases are wholly separate and distinct clinical entities. For purposes of diagnosis and treatment, they will be considered individually.

GONORRHEA

At the beginning of World War II, there was probably no prevalent disease comparable to gonorrhea in the wide disparity between the therapeutic recommendations of the experts and the care usually accorded the average patient. Fortunately, the new methods of treatment were so simple that by the end of the war the management of gonorrhea in the Army followed in large measure the directives prepared by the experts and issued by The Surgeon General.

Prior to the publication of Circular Letter No. 18, there was little or no uniformity of practice in the diagnosis and treatment of gonorrhea by medical officers. The older officers of the Regular Army Medical Corps, who had been trained in the disciplines described by Siler, had in general advanced to supervisory or administrative positions; the medical officers who were actually treating the patients were young physicians from civilian practice. Each of these groups had had different training and experience; most of them had little or no special knowledge of the management of patients with gonorrhea and few knew little more about the opinions of the experts than a dim awareness that the relatively new sulfonamide drugs were useful in treatment.

Circular Letter No. 18 brought a semblance of order out of the chaos which these conditions had fostered. The Army was rapidly expanding, but with unimportant exceptions, the troops were stationed in training camps within the continental United States. These camps were adequately supplied

with cantonment-type hospitals, in which it was usual practice to have venereal disease wards to which an adequate number of medical officers were permanently assigned. All patients with gonorrhea were hospitalized, so that they came under the care of a relatively small group of medical officers. Accordingly, the information contained in Circular Letter No. 18 had to be disseminated to only a relatively small number of medical officers, many of whom had had no previous training in the management of gonorrhea, but all of whom, actually or from necessity, had a special interest in the problem. This point is important because the contrasting situation will be brought out later in the discussion of the treatment of gonorrhea on a duty status.

It was the consensus of observers during 1941 and 1942 that in general a determined and satisfactory effort was made to carry out the provisions of Circular Letter No. 18. The observed deviations were most frequently carelessness in diagnostic technique, for example, preparation and examination of smears by a relatively untrained technician using only methylene blue for staining; a tendency to prescribe larger total doses of the sulfonamides than recommended, either by giving greater individual doses or, more commonly, by a longer course of treatment; and the early and often vigorous use of local methods of treatment, especially urethral irrigation, prostatic massage, and the passage of sounds.

The provisions of Circular Letter No. 18 with regard to the diagnosis and treatment of gonorrhea are of more than passing interest. Under the heading entitled "Diagnosis in the Male," the circular says "a diagnosis of gonorrhea must not be made in the absence of laboratory confirmation * * *," although it does provide for emergency treatment without diagnosis in case laboratory facilities are not readily available. The section on the diagnosis in the female is much less definitely phrased and contains the clear implication that the history of exposure to a known case of gonorrhea may be utilized as presumptively supporting the diagnosis.

The regimen recommended for the treatment of acute gonorrhea consisted of 19 gm. of sulfathiazole to be given in 10 days (3 gm. the first day, 2 gm. daily thereafter) in cases which responded well; if the clinical response to sulfathiazole was not satisfactory by the fifth day, sulfapyridine (3 gm. the first day, 2 gm. daily thereafter) was substituted. If this exchange proved beneficial by the 10th day, this drug was continued until a total of 15 days of chemotherapy (5 days of sulfathiazole, 10 days of sulfapyridine) had been given. If the clinical response to this regimen was not good, the patient was to be transferred (presumably to a general hospital) for special care.

The test of cure advised for the male was based upon the examination of gram-stained smears of material expressed by prostatic massage done weekly for 8 weeks. The use of culture was mentioned, but not emphasized. The test of cure advised for the female was based on smear from the urethra, cervix, and Skene's and Bartholin's glands every 2 weeks for 3 months, with cultures from the same areas monthly on the last day of the menstrual period.

The recommended followup for both sexes included one serologic test for syphilis done 3 to 4 months after the original infection with gonorrhea.

With the deviations noted, these procedures were followed for over a year, but in the winter of 1941–42, Dr. P. S. Pelouze, directly representing The Surgeon General, made personal visits to a number of the larger Army camps, and his report occasioned The Surgeon General to write to the chairman of the National Research Council, in part, as follows: "Dr. P. S. Pelouze has just presented to us some evidence that the recommendations of the Council on the treatment of gonorrhea may need revision in the light of recent advances in this field * * *."[4]

Accordingly, a revision of Circular Letter No. 18 was considered and approved by the Subcommittee on Venereal Diseases in March 1942, and this eventually appeared in Circular Letter No. 74, Office of the Surgeon General, 25 July 1942. The important changes included alteration of the criteria for diagnosis of gonorrhea in the female to bring them into line with those previously defined for the male; the recommendation of sulfathiazole or sulfadiazine as the drug of choice to be administered in a dose of 4 gm. daily for 5 days, this course to be repeated no more than once; the direction that if sulfapyridine must be used it be given in a dose of only 3 gm. daily for 5 days; a relaxation of the test of cure; a marked reduction in the period of followup (3 weeks advised, but not insisted upon); and finally the recommendation "* * * that carefully selected patients with sulfonamide-resistant infections be given ten hours of sustained fever therapy * * *" without, however, directions or suggestions as to how the selection should be made. This deficiency was partially rectified by Circular Letter No. 86, Office of the Surgeon General, 18 August 1942, which designated eight named general hospitals as fever therapy centers and implied that the final decision as to whether the patient should be treated with fever should be left to the staff of the hospital to which he was referred for this treatment.

These eight hospitals soon proved to be insufficient to care for the mounting load of patients with sulfonamide-resistant gonorrhea. The average rate of cure with the sulfonamides was falling below 75 percent, owing to the development of sulfonamide-resistant strains of the gonococcus and to the substantial number of chronic cases that probably represented relapse after inadequate self-administered treatment. Every station and general hospital had a mounting backlog of patients with chronic gonorrhea for whom the only prospect of cure and return to duty at that time lay in treatment with fever. Accordingly, at the request of The Surgeon General, a conference was held on 6 April 1943, under the auspices of the Subcommittee on Venereal Diseases on the use of combined fever and chemotherapy in the treatment of sulfonamide-resistant gonorrhea. The aim of the conference was to prepare a draft of a circular letter to be sent out by the Surgeon General's Office to

[4] Minutes, Fourteenth Meeting, Subcommittee on the Venereal Diseases, National Research Council, 11 Mar. 1942.

appropriate military hospitals. The draft was approved by the Subcommittee on Venereal Diseases on 7 April 1943, forwarded to The Surgeon General, and published as Circular Letter No. 97, Office of the Surgeon General, 12 May 1943. This broadened the base of the number and type of hospitals authorized to administer fever therapy to patients with sulfonamide-resistant gonorrhea and at the same time protected the patient by defining with great care the criteria for the selection of patients and details for management of therapy. It had been found that one session of 8 hours at approximately 106° F. (rectally) would accomplish cure in about 90 percent of patients with sulfonamide-resistant gonorrhea, that half of the failures would achieve a satisfactory result from a second similar treatment, but that fever in excess of two such bouts apparently was valueless. No patient, therefore, was to be subjected to more than two 8-hour sessions of induced fever, even though manifestations of the disease persisted.

Not long afterward, Circular Letter No. 129, Office of the Surgeon General, 22 July 1943, amended Circular Letter No. 74 in two important particulars. It pointed out that prostatic massage should not be done as a test of cure of acute gonorrhea and, thereby, served to prevent a substantial number of relapses and complications occasioned by this procedure. It advised that for patients with gonorrhea treated in hospital the dose of sulfathiazole or sulfadiazine should be increased to a total of 33 gm., given as an initial dose of 4 gm. followed by 1 gm. every 4 hours night and day of 5 days. This, it was hoped, would somewhat reduce the number of sulfonamide failures.

Treatment on duty status.—Prior to the advent of chemotherapy, it had been the custom in the Army to hospitalize soldiers for the treatment of gonorrhea,[5] in spite of the fact that the vast majority of civilian patients with gonorrhea were treated on an ambulatory basis. The reasons given for this are well known: The Army in peacetime felt it impracticable to assign a light-duty status, the philosophy being that the soldier either was able for full duty or belonged in the hospital. During World War I, however, working quarantine was extensively employed for the treatment of selected cases of gonorrhea (especially the chronic and recalcitrant), and this procedure was later authorized by paragraph 7, AR (Army Regulations) 40–235, 11 October 1939. Quoting this regulation as authority, Circular Letter No. 18, 10 March 1941, said in part: "Even under ambulatory conditions, acute gonorrhea may be cured by appropriate measures in a large proportion of cases. Therefore, when considered desirable and local conditions permit, acute gonorrhea may be treated on an ambulatory basis in working quarantine." However, very little use was made of working quarantine or ambulatory treatment. Accordingly, Circular Letter No. 74, 25 July 1942, dealt realistically with the matter, as follows: "In the Zone of Interior and in the communications zone, venereal disease cases will ordinarily be hospitalized for treatment during the infectious stages. In order to maintain effective strength of organ-

[5] See footnote 2, p. 409.

izations during combat, consideration may be given to the treatment of veneral disease cases on a duty status with their organization in the combat zone."

In the meantime, however, dissatisfied both with the large number of hospital beds occupied by patients with gonorrhea and with the loss of time from training, certain posts in the Fourth Service Command (Camp Forrest, Tenn., was apparently the first) had undertaken the treatment of gonorrhea with the sulfonamide compounds on a duty status. The method seemed to work and, if it could be shown to be therapeutically efficient, might be used more widely. Accordingly, in November 1942, a board[6] was appointed to evaluate the experiences which had so far been gained.[7] The board members proceeded from the Office of the Surgeon General to posts within the Fourth Service Command where gonorrhea was being treated on a duty status. Their report recommended (1) that the policy of treating uncomplicated gonorrhea on a duty status be approved and that the adoption of such a policy wherever feasible be encouraged and (2) that because this method may not be equally practicable under all conditions its adoption not be made mandatory.

The recommendations made by this board were officially authorized in January 1943,[8] and on 1 February 1943, Circular Letter No. 32, Office of the Surgeon General, gave in detail directions for the management of patients with acute gonorrhea while ambulatory.

Following this, the duty-status treatment of acute gonorrhea was undertaken on a large scale, both in the continental United States and in the oversea theaters, but the sulfonamides were so quickly thereafter replaced by penicillin that there was no opportunity to gain a large-scale evaluation of the usefulness of the method. Even a complete study, however, would have been difficult to evaluate unless the ambulatory method were a marked improvement over treatment in hospital. This is because of the declining percentage of cures already being observed among hospitalized patients and the great variation in the interest, training, and experience of the large number of unit medical officers who suddenly became responsible for the diagnosis and treatment of gonorrhea and for the evaluation of results.

Penicillin.—The verbal report, early in 1943 (subsequently published in September 1943), by Mahoney and his collaborators,[9] on the use of penicillin in the treatment of sulfonamide-resistant gonorrhea, rapidly removed the

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[6] The board was composed of Brig. Gen. Henry C. Coburn, Jr.; Col. (later Brig. Gen.) Hugh J. Morgan, MC; Lt. Col. (later Col.) Thomas B. Turner, MC; Col. Alvin L. Gorby, MC; and Maj. (later Lt. Col.) Robert Dyar, MC.

[7] (1) Letter, Col. John A. Rogers, MC, Executive Officer, Office of the Surgeon General, to Commanding General, Headquarters, Services of Supply, 19 Nov. 1942, subject: Appointment of Board for Investigation of the Treatment of Venereal Disease on a Duty Status. (2) Letter, J. F. McGuire, The Adjutant General's Office, to The Surgeon General, 30 Nov. 1942, subject: Board of Officers.

[8] War Department Memorandum W40-2-43, Treatment of Individuals With Uncomplicated Gonorrhea on Duty Status, 19 Jan. 1943.

[9] Mahoney, J. F., Ferguson, C., Buchholtz, M., and Van Slyke, C. J.: The Use of Penicillin Sodium in the Treatment of Sulfonamide-Resistant Gonorrhea in Man. Am. J. Syph., Gonor. & Ven. Dis. 27: 525-528, September 1943.

practical importance of determining the best way of treating with sulfonamide. It appeared that penicillin in almost any dosage effected cure in a high percentage of cases and in almost miraculous fashion. This was confirmed by Herrell and his coworkers.[10]

This promise of a solution for an increasingly harrassing problem of the soldier led, in May 1943, to a clinical investigation in 15 Army hospitals of the use of penicillin in the treatment of this condition. Within a relatively short time, results of the treatment with penicillin of 1,686 patients with sulfonamide-resistant gonorrhea were available. The details of this study were later published by Sternberg and Turner.[11] All of the 1,686 patients were men; their ages reflected the usual distribution in the Army at the time; they had had on the average 58 gm. of a sulfonamide ending at least 5 days before penicillin was administered, and 236 had also had treatment with fever. The patients were divided into groups, each group treated with a different dose of penicillin. With a dose of 160,000 units or more, 98 percent of the patients achieved cure; as the dose was reduced below 100,000 units, the cure rate fell off rapidly. There were in all (regardless of dosage) 126 failures. Of these, 85 were re-treated, all with 100,000 units and 91.8 percent of them were cured. This raised the overall cure rate for two courses of treatment to 99 percent.

These dramatic results induced The Surgeon General, on 23 September 1943, to address a letter to the service command surgeons authorizing the use of penicillin in the treatment of sulfonamide-resistant gonorrhea. The dosage authorized was 50,000 units in doses of 10,000 units at 3-hour intervals, with permission to re-treat with 100,000 units administered in 10,000-unit doses hourly in case of failure of the first course. It must be recalled that penicillin was in excessively short supply at the time, a fact that seriously influenced the size of the dose recommended. As the supply improved, this was increased to 100,000 units given in 20,000-unit doses by TB MED (War Department Technical Bulletin) 9, 12 February 1944. About a month later, 6 March 1944, TB MED 16 authorized the use of penicillin for the treatment of sulfonamide-resistant gonorrhea in station hospitals and directed that it should be administered to patients with gonorrhea immediately after failure to respond to one course of a sulfonamide.

As the supply of penicillin increased, its use was extended. On 21 September 1944, TB MED 96 provided for complete replacement of sulfonamides by penicillin in the treatment of gonorrhea, except for those individuals who failed to respond to penicillin. This bulletin said further that the treatment of uncomplicated gonorrhea with penicillin might be carried out as a hospital or dispensary procedure, but recommended that where satisfactory medical facilities were available hospitalization be avoided. The recommended dose

[10] Herrell, W. E., Cook, E. N., and Thompson, L.: Use of Penicillin in Sulfonamide Resistant Gonorrheal Infections. J.A.M.A. 122: 289-292, 29 May 1943.

[11] Sternberg, T. H., and Turner, T. B.: The Treatment of Sulfonamide Resistant Gonorrhea With Penicillin Sodium: Results of 1,686 Cases. J.A.M.A. 126: 157-161, 16 Sept. 1944.

was 100,000 units, given in 20,000-unit injections intramuscularly every 3 hours for those in hospital, or five injections spaced over an 8-hour period for outpatients. In the event of failure, re-treatment with the same dose was suggested, and if the failure persisted, a third course of treatment with 300,000 units given in 20,000-unit injections at 3-hour intervals was advised. In the event of failure of these three courses of penicillin, the treatment of choice would be sulfathiazole in the 33-gm. dose recommended by Circular Letter No. 129. Finally, TB MED 196, 20 August 1945, redefined the criteria for diagnosis and cure and increased the initial dose of penicillin to 200,000 units administered in four injections of 50,000 units every 2 to 3 hours, depending on whether the patient was hospitalized or being treated on duty status. Patients failing of cure after the first course were to be re-treated similarly with 200,000 units. Those patients who did not respond to these two courses were to be hospitalized for more complete urological and bacteriological investigation and, if gonococcal infection were proved, to be given at least 500,000 units of penicillin in 50,000-unit doses every 2 or 3 hours.

It was at first feared that, with the widespread use of penicillin in the treatment of gonorrhea, the gonococcus might develop penicillin resistance analogous to the sulfonamide resistance already encountered. None of the Army material, however, has proved any evidence to that effect, either clinically or in vitro, although the production of penicillin resistance in vitro has been reported by Dr. Joseph E. Moore.[12] As further experience was gained, it became clear that 10 to 15 percent of patients with gonorrhea failed to respond to 100,000 units of penicillin but that most, if not all, would respond to repeated courses or increased doses. Toward the close of World War II, several cases were reported in which penicillin resistance was suspected clinically, but it was not determined whether these failures of treatment were due to true penicillin-resistant strains, to insufficient, deteriorated, or substandard penicillin, or to failure to detect the true etiological agent, thereby confusing gonorrhea with nonspecific urethritis.

And so the end of the war saw a therapeutic triumph. Penicillin in adequate dosage had solved the problem of sulfonamide-resistant gonorrhea, had provided a substitute for dangerous, troublesome, and unpleasant fever therapy, had relieved general hospitals of rapidly increasing numbers of patients with gonorrhea, and had made of the disease a relatively minor infection, with few complications and with a small noneffective rate. In 1937, complications developed in about one-fourth of all cases of gonorrhea in the U.S. Army; in 1944, complications occurred in approximately 1 percent of all cases.[13]

Penicillin in oil-beeswax.—One remaining difficulty was the fact that the only effective method for the administration of penicillin then known was by

[12] Moore, Joseph Earle: Penicillin in Syphilis. Springfield, Ill.: Charles C Thomas, 1946.

[13] Monthly Progress Report, Army Service Forces, War Department, 28 Feb. 1945, Section 7: Health.

injection, preferably intramuscular; yet in the usual aqueous or saline solution, penicillin was so rapidly absorbed and excreted that in order to maintain therapeutically effective blood levels [14] it had to be given no less frequently than every 3 hours.[15] A number of investigators had approached this subject—one group attempting to delay excretion by blocking the kidney;[16] others, to delay absorption by local vasoconstriction [17] or by local application of ice packs.[18] None of these methods was particularly successful. The first satisfactory method for delaying the absorption of penicillin with relative uniformity was devised by Romansky and Rittman at the Walter Reed General Hospital, Army Medical Center, Washington, D.C. These investigators found the injection of a suspension of 300,000 units of penicillin, preferably the calcium salt, in 1 cc. of a vehicle consisting of peanut oil containing 4.8 percent by weight of beeswax, was followed by assayable blood levels of penicillin from 24 to 36 hours after injection [19] and produced excellent therapeutic results in patients with acute gonorrhea.[20]

The Surgeon General then initiated an investigation of the subject to be carried out, both clinically and in the laboratory, at the Regional Hospital, Fort Bragg, N.C. Partial confirmation of the results of the original investigators was achieved. Over 90 percent of 88 patients with acute gonorrheal urethritis were cured with a single intramuscular injection of 300,000 units of calcium penicillin suspended in the oil-beeswax vehicle.[21] The substance was not entirely without its objectionable features, however. Uniform blood levels were not always obtained, and after appropriate investigation these later investigators concluded that the blood levels produced depended on both

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[14] In October 1948, the previously accepted concept that assayable levels of penicillin concentration in the blood must be maintained in order to gain maximum therapeutic effect was being sharply questioned. At the time of the development of POB (penicillin in oil-beeswax), however, there was general acceptance of the concept that maintenance of a relatively uniform concentration of penicillin in the blood was necessary for maximum therapeutic effect.

[15] Rammelkamp, C. H., and Bradley, S. E.: Excretion of Penicillin in Man. Proc. Soc. Exper. Biol. & Med. 53: 30–32, May 1943.

[16] Beyer, K. H., Woodward, R., Peters, L., Verwey, W. F., and Mittis, P. A.: Prolongation of Penicillin Retention in Body by Means of Para-Aminohippuric Acid. Science 100: 107–108, 4 Aug. 1944.

[17] Parkins, W. M., Wiley, M., Chandy, J., and Zintel, H. A.: Maintenance of the Blood Level of Penicillin After Intramuscular Injection. Science 101: 203–205, 23 Feb. 1945.

[18] Trumper, M., and Hutter, A. M.: Prolonging Effective Penicillin Action. Science 100: 432–434, 10 Nov. 1944.

[19] Romansky, M. J., and Rittman, G. E.: Method of Prolonging Action of Penicillin. Science 100: 196–198, 1 Sept. 1944.

[20] (1) Romansky, M.J., and Rittman, G. E.: Penicillin: Prolonged Action in Beeswax-Peanut Oil Mixture; Single Injection Treatment of Gonorrhea. Bull. U.S. Army M. Dept. No. 81: 43–49, October 1944. (2) Romansky, M. J., Murphy, R. J., and Rittman, G. E.: Single Injection Treatment of Gonorrhea With Penicillin in Beeswax-Peanut Oil; Results in 175 Cases. J.A.M.A. 128: 404–407, 9 June 1945.

[21] (1) Kirby, W. M. M., Leifer, W., Martin, S. P., Rammelkamp, C. H., and Kinsman, J. M.: Intramuscular and Subcutaneous Administration of Penicillin in Beeswax-Peanut Oil. J.A.M.A. 129: 940–944, 1 Dec. 1945. (2) Leifer, W., Martin, S. P., and Kirby, W. M. M.: The Treatment of Gonococcal Urethritis With Single Injections of Penicillin-Beeswax-Peanut Oil Mixtures. New England J. Med. 233: 583–586, 15 Nov. 1945. (3) Kirby, W. M. M., Martin, S. P., Leifer, W., and Kinsman, J. M.: Maintenance of Therapeutic Blood Concentrations of Penicillin for Twenty-four Hours Following Single Injections of Penicillin-Beeswax-Peanut Oil Mixtures. J. Lab. & Clin. Med. 31: 313–316, March 1946.

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the concentration of penicillin in the vehicle and the total amount administered. They also found the mixture so viscid as to require incubation at 37° C. to go through a 17-gage needle and so immiscible with water that the slightest amount of moisture in the syringe would produce a completely unmanageable gummy, sticky mass. As the war ended, it seemed that the preparation represented a large step forward but that several improvements, even perhaps an entire alteration of its composition, would be necessary before it would be suitable for widespread adoption.

NONSPECIFIC URETHRITIS

Although not officially classified as one of the venereal diseases, nonspecific urethritis[22] bears consideration here because of its close association with gonococcal urethritis, both because of its etiology and because of the diagnostic confusion which it so often produced. The condition was common, amounting in various experiences from 10 to 40 percent of all cases of urethritis, but unfortunately it was never subjected to careful study. The diagnosis was made entirely by the exclusion of gonorrhea, and treatment usually began with the method that currently was being employed in the management of gonorrhea. This was commonly unsuccessful, in which case the patient was referred to the urologist and subsequently treated by various manipulative procedures at the physician's direction. These were also frequently unsuccessful, and eventually the process was allowed to run its natural course, which tended to be one of great chronicity. There probably was no disease of comparable numerical importance during World War II that was so completely neglected both as to definition of etiology and as to development of satisfactory methods of treatment.

SYPHILIS

Before and during the early stages of mobilization, that is, prior to the publication of Circular Letter No. 18, 10 March 1941, the diagnosis and treatment of early syphilis in the Army essentially followed the recommendations of the Cooperative Clinical Studies Group[23] as elaborated in the standard textbooks.[24] Neoarsphenamine was the arsenical drug most commonly employed; many bismuth compounds were used, although a suspension of the subsalicylate in oil was perhaps the most frequently employed; and rest periods by either design or accident tended to be more common than the experts would advise. On the whole, however, standards of practice compared favor-

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[22] There is no useful source material on nonspecific urethritis in the official records. The material on which this section is based was assembled by Col. Paul Padget, MC, from conversations with many medical officers from 1942 to 1945 and recorded in his personal diary.

[23] Cooperative Clinical Studies in the Treatment of Syphilis; Early Syphilis. Ven. Dis. Inform. 13: 207–231, 20 June 1932; 253–293, 20 July 1932.

[24] (1) Moore, Joseph Earle: The Modern Treatment of Syphilis. Springfield, Ill.: Charles C. Thomas, 1933. (2) Stokes, John H.: Modern Clinical Syphilology. 2d edition. Philadelphia: W. B. Saunders Co., 1934.

ably with those of the average health department clinic at the time. As in health department clinics, however, there was much less uniformity of practice in the management of the various forms of late syphilis, and from a review of old records, one has the impression that many medical officers treating patients with late syphilis were actually treating the positive blood test rather than the patient. For this, of course, the medical officers concerned should not be blamed since it was then, and unfortunately still is, likewise common in civilian practice.

In supplying the material upon which Circular Letter No. 18 was based (p. 409), the Subcommittee on Venereal Diseases made no recommendations concerning the management of syphilis which were peculiar to the Army. Instead, this material represented simply a summary of accepted good practices in the diagnosis and treatment of syphilis which were then current in best civilian practice. In this circular letter, accuracy of diagnosis was emphasized; necessity for clocklike regularity of treatment was reiterated; Mapharsen (oxophenarsine hydrochloride), at that time the only commercially available arsenoxide, was recommended as the arsenical drug of choice; and treatment at weekly intervals was to be continued for 15 to 18 months.

The 18-month system of treatment was impracticable even under the relatively static conditions of training. In view of the extent to which all practical administrative difficulties would be magnified in an oversea theater, particularly after combat was joined, the need for a shorter method for the treatment of syphilis became obvious. Accordingly, representatives from the Office of the Surgeon General had informal meetings with members of the Subcommittee on Venereal Diseases, and at a formal meeting on 27 May 1942, the subcommittee approved recommendations made by this subgroup. These were published in Circular Letter No. 74, 25 July 1942.

The principles of accurate diagnosis and the criteria for cure were not significantly changed from the form in which they appeared in Circular Letter No. 18, but the treatment scheme was compressed into 40 doses of Mapharsen and 16 doses of bismuth given over a 6-month period. By this system, Mapharsen was given in two courses of 20 injections, each twice weekly for 10 weeks separated by 6 weeks of therapy with bismuth, the additional bismuth being given in two groups of five weekly doses concurrently with the beginning of the first and the end of the second courses of Mapharsen.

According to Sternberg and Leifer,[25] this treatment system was used in the management of approximately 200,000 soldiers with syphilis, with a mortality rate ascribable to treatment of about 0.003 percent. In a study of the short-term results in 3,000 soldiers with early syphilis, 72 percent of whom had been observed for more than 1 year after the completion of the 26-week treatment, they say " * * * the results appear excellent with satisfactory progress in 98.25 percent of seronegative primary, 94.48 percent of seroposi-

[25] Sternberg, T. H., and Leifer, W.: Treatment of Early Syphilis by Twenty-six-Week Mapharsen-Bismuth Schedule. Am. J. Syph., Gonor. & Ven. Dis. 31: 124–134, March 1947.

tive primary, and 89.34 percent of secondary cases. There were but 18 (0.64 percent) abnormal cerebrospinal fluids among the 2,842 examined."

Intensive arsenotherapy.—As the war progressed, this treatment scheme, later shown to be therapeutically effective by Sternberg and Leifer, became increasingly impractical. Six months under the pressure of war was, comparatively speaking, longer and more intolerable than 18 months in peacetime; biweekly injections for 20 of the 26 weeks interfered even with military training. Maintenance of uninterrupted medical control for the time necessary to complete treatment became increasingly difficult. Only 38 percent of the troops with syphilis registers who came to the European theater during March 1943 had had as much as two-thirds of the optimal amount of treatment up to the time of their embarkation.[26] None had been treated in transit, which often had imposed an additional lapse of many weeks. Consequently, there was widespread pressure to persuade the Army to adopt one or another of the rapid treatment systems which were in use or could be made available. The 5-day intravenous drip method[27] was particularly strongly urged because this scheme, unlike other proposed methods, had had considerable clinical use just prior to this time. The Subcommittee on Venereal Diseases reviewed the subject in detail on 13 January 1942 and 10 June 1943, and it was taken under advisement by the Committee on Medicine, National Research Council, 16 October 1942. This committee concluded:

That the intensive arsenotherapy of early syphilis (including the five-day intravenous drip method) be considered as still in the experimental stage; that the optimum time-dose relationship still requires to be established by further animal and subsequent clinical experimentation; and that at present the method cannot be recommended for routine use by the Armed Forces.

The need for a rapid treatment method was so great, however, especially in oversea theaters (fig. 56), that at its 19th meeting, 10 June 1943, the Subcommittee on Venereal Diseases bowed to the continuing pressure of the advocates of the 5-day intravenous drip technique and passed a series of recommendations which had been made at a conference on intensive arsenotherapy of early syphilis held on 19 May 1943. These recommendations read in part, as follows:

1. Owing to the relatively high mortality rate, no system of intensive arsenotherapy compressed into a period of 2 weeks or less is as yet suitable for routine adoption by the Armed Forces.

2. For the routine treatment of early syphilis in the Armed Forces the 26-week system now in use in the U.S. Army should be continued pending further information concerning intensive treatment systems.

3. It is hoped that the U.S. Public Health Service will amplify a statistical evaluation of the several methods of intensive arsenotherapy of early syphilis * * *.

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[26] Annual Report, Senior Consultant in Dermatology, Office of the Chief Surgeon, European Theater of Operations, U.S. Army, 1943.

[27] Leifer, W., Chargin, L., and Hyman, H. T.: Massive Dose Arsenotherapy of Early Syphilis By Intravenous Drip Method: Recapitulation of Data (1933 to 1941). J.A.M.A. 117: 1154–1160, 4 Oct. 1941.



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FIGURE 56.—Poisoning by Mapharsen in treatment of syphilis. Fixed arsenical eruption on left side of face, neck, chest, *and thigh of 6 months'* duration. Patient was treated at the 20th General Hospital, China-Burma-India theater, June 1943.

4. In oversea areas, whether advanced training or combat zones, two alternative methods of intensive arsenotherapy of early syphilis, treatment compressed within a period of 2 weeks or less, may be utilized provided: (a) That patients be treated under hospitalized conditions rather than on an ambulatory basis, and (b) that treatment be administered under the direction of specially qualified personnel.

The two treatment systems recommended for early syphilis were the 5-day intravenous drip and 10-day multiple syringe technique. It was further suggested that the same intensive treatment systems might be utilized in the continental United States for selected personnel under the same conditions. An alternative 12-week system was advised in the event that hospitalization was not practicable. Detailed descriptions of the techniques of the three systems were provided.

In the Surgeon General's Office, it was decided to give this scheme an experimental trial in one large hospital before recommending it for general use in the Army, even in oversea theaters. Accordingly, in July 1943,[28] a research project was set up at Fort Bragg on the use of intensive doses of Mapharsen by intravenous drip.[29] The experiment was terminated in Octo-

[28] Memorandum, Lt. Col. Thomas B. Turner, Chief, Venereal Disease Control Branch, Preventive Medicine Division, for General Kirk, 3 July 1943, subject: Short, Intensive Treatment of Syphilis.

[29] Fort Bragg was selected not only because of its size but because Capt. (later Maj.) Williard Leifer, MC, joint author of the original and numerous other papers on the 5-day intravenous drip technique was on duty there.

ber 1943, when the superiority of penicillin became obvious. No new information was obtained from study of the patients treated up to that time.

In the meantime, in the Office of the Chief Surgeon, European theater (which was, because of the disrupted state of communications, virtually isolated from knowledge of current developments in the Surgeon General's Office), it had been decided to try an entirely new scheme for the treatment of syphilis with Mapharsen. It was undertaken because of the utter impossibility of even approximately regular treatment under the existing conditions. Consideration was given to the known facts regarding the toxicity of Mapharsen as determined by the time-dose relationship. Theoretical considerations and experimental work with rabbit syphilis, culled from the most recent source material available on massive arsenotherapy, indicated that the total curative dose of Mapharsen for early syphilis in the human should be of the order of 20 mg. per kilogram of body weight.[30] Further, it appeared that the incidence of reactions is determined almost entirely by the time-dose relationship, with a very rapid rise in rate as the total interval for treatment is decreased, becoming intolerable if the treatment interval is reduced significantly below 5 days, but not decreasing with particular rapidity as the span of treatment is increased above 20 days.

With this information, and in consideration of the practical military problems involved, it was decided, for the patient with early syphilis, to give clinical trial to the following scheme of treatment: One mg. of Mapharsen per kilogram of body weight (but not to exceed a single dose of 75 mg.) was to be given by syringe daily for 20 days. The choice of a 20-day treatment scheme was not only convenient, as it allowed doses of 1 mg. per kilogram per day to total 20 mg. per kilogram in 20 days, but was also determined by sound theoretical consideration.[31] The treatment was carried on in hospital; the patient was carefully observed both clinically and by laboratory tests. In addition to the Mapharsen, he was given at regular intervals 8 doses each of 0.2 gm. of bismuth subsalicylate suspended in oil; that is, approximately a dose of bismuth every other day.

Over 4,000 patients were treated by this method in the European theater, with no deaths. The treatment was completed in 96.3 percent of the first 775 patients and in a somewhat higher percentage of the remainder. In one series of 1,343 consecutive cases of early syphilis treated by the 20-day form of intensive arsenotherapy, results of serological tests for syphilis were reported after 6 or more months in 982. In 258, followup reports were received more than a year after completion of therapy. Ninety-five percent of both groups had a negative serological test and a normal cerebrospinal fluid at the time of last examination. The time relations of the observed serological relapses were such, however, that approximately twice as many definitely un-

[30] Moore, Joseph Earle: The Modern Treatment of Syphilis. 2d edition. Springfield, Ill: Charles C Thomas, 1943.

[31] See footnote 26, p. 420.

satisfactory results were noted at the end of 12 months as at the end of 6 months after treatment.

The authors who reviewed this material concluded[32] that the 20-day scheme for intensive arsenotherapy will yield very satisfactory 1-year results in the treatment of early syphilis but that when compared to penicillin or penicillin plus chemotherapy given on a less toxic schedule it carries an unjustifiable risk. This is illustrated[33] by an analysis of 500 consecutive patients who were treated by this method. Four hundred and seventy six of these eventually completed the treatment, sometimes with delays necessitated by minor reactions, but in 24, or 4.8 percent, the procedure had to be abandoned because of severe reactions. Seven of these patients had definite signs of cerebral irritation, and two more presented the classical picture of hemorrhagic encephalitis. Jaundice occurred in six, toxemia and agranulocytosis in three each, while severe fever occurred in two and severe albuminuria in one.

Penicillin.—In June of 1943, Mahoney and his collaborators treated four sailors with early syphilis with penicillin in a dose of 1.2 million units which they had calculated as being the theoretical optimum[34] from observations on experimental animals. The results were so dramatic that the experiment was immediately extended within the limits imposed by the short supply of penicillin at that time.

This information spread rapidly, largely by word of mouth (all the data concerning penicillin were then classified information). At the 20th meeting of the Subcommittee for Venereal Diseases on 29 September 1943, "It was agreed that the clinical and experimental evidence so far available justified an extensive trial of penicillin in human beings * * *," and recommendations were passed for the formation of a penicillin panel, under the National Research Council, to coordinate experimental and clinical trials of penicillin in humans with syphilis which were to be conducted by appropriate facilities of the Army, the Navy, the U.S. Public Health Service and eight[35] participating civilian clinics. At the first meeting of the penicillin panel a month later, six treatment schedules for investigation were agreed upon. Five of these were to be undertaken immediately, one was deferred because of the shortage of penicillin, and the Army agreed to contribute observations upon

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[32] Pillsbury, D. M., and Loveman, A. B.: Six- to Twelve-Month Follow-Up Results in Early Syphilis Treated by a Twenty-Day Intensive Arsenobismuth System. Am. J. Syph., Gonor. & Ven. Dis. 31: 115-123, March 1947.

[33] Cormia, F. E., and Blauner, S. G.: Reactions to Twenty-Day Intensive Therapy With Mapharsen and Bismuth for Syphilis With a Note on the Use of BAL in Their Management. Am. J. Syph., Gonor. & Ven. Dis. 31: 135-149, March 1947.

[34] Mahoney, J. F., Arnold, R. C., and Harris, A.: Penicillin Treatment of Early Syphilis: A Preliminary Report. Ven. Dis. Inform. 24: 355-357, Dec. 1943; also Am. J. Pub. Health 33: 1387-1391, December 1943.

[35] The number was greatly increased later, so that at one time there were nearly 40 clinics participating.

120 patients treated by two of these schedules within the first 3 months of the experiment.[36]

From this point (October 1943), the development of the use of penicillin in the treatment of syphilis was essentially a civilian activity, the history of which has been summarized in detail by Moore. The Army continued to participate in the clinical investigations on a small scale, but it was quite properly much more concerned with the application of this new, safe, and simple therapeutic method on a mass treatment scale than in attempting clinical investigative work.

On 5 April 1944, Brig. Gen. James S. Simmons, Chief, Preventive Medicine Service, Office of the Surgeon General, addressed the following letter to Dr. Moore, Chairman, Subcommittee on Venereal Diseases, National Research Council:

> It is desired that the Subcommittee on Venereal Diseases, National Research Council, consider at its April 20th [1944] meeting the present state of knowledge of the penicillin treatment of syphilis in relationship to its suitability for application to Army practice. The present prolonged treatment schedules place a great chore on the Medical Department and interfere seriously with training and combat. Furthermore, in active Theaters of Operation it is impossible to maintain any degree of regularity in administering treatment.
>
> For these reasons The Surgeon General would appreciate an expression of opinion of the Subcommittee on Venereal Diseases as to the earliest possible time penicillin treatment of syphilis may be applied to Army practice.

This was a staggering request. Arsphenamine and its derivatives had been employed in the treatment of syphilis for nearly 35 years without reaching satisfactory agreement on the details of its utilization, yet here was a request for advice regarding the large-scale application of an entirely new therapeutic agent which had first been used in the treatment of syphilis only 9 months before and with which experience on any statistically significant scale was only 6 months old. Well aware of the magnitude of the responsibility being assumed, but equally aware of the problems confronting the Army, the minutes of the 22d meeting of the Subcommittee on Venereal Diseases, 20 April 1944, merely say:

> The purpose of the request and its relationship to campaign conditions was further amplified in general discussion. This led to the following recommendation: It is recommended that in active theaters of operation the penicillin treatment of early syphilis (i.e., infections of less than one year's duration, whether or not partially treated with arsenical chemotherapy) be adopted immediately. The minimum total dosage of penicillin should be 2.5 million units, given over an eight-day period, administered in 64 intramuscular injections every three hours day and night. It is further desirable that such penicillin treated patients be followed without subsequent antisyphilitic treatment (unless in the event of clinical or serologic relapse) as frequently as is practicable and that all such cases be thoroughly resurveyed as to syphilis prior to separation from the service.

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[36] Minutes, Conference on Penicillin in the Treatment of Syphilis in Human Beings by a Panel Composed of Members of the Subcommittee on Venereal Diseases and the Committee on Chemotherapeutics and Other Agents, National Research Council, 29 Oct. 1943.

A subsequent letter from The Surgeon General to the commanding generals of the oversea theaters for the attention of the chief surgeon summarized current knowledge of the use of penicillin in the treatment of syphilis and directed (1) that all new cases of primary and secondary syphilis be treated with penicillin, (2) that the schedule of treatment be 40,000 units intramuscularly every 3 hours for a total of 60 doses or 2.4 million units for each case, and (3) that followup examinations should be obtained at monthly intervals for a minimum period of 1 year.[37]

The receipt of this directive in the European theater coincided almost exactly with the date of the invasion of continental Europe. It was, therefore, particularly welcome in the attempt to provide facilities for proper diagnosis and treatment of the venereal diseases, especially syphilis, within the Army areas. Evacuation and the loss of a trained soldier to his organization was to be avoided, but at the same time it was important not to increase the patient load which must be carried by field or evacuation hospitals. Accordingly, venereal disease treatment centers were planned within the Army areas staffed by at least one medical officer with experience and ability in the diagnosis and treatment of the venereal diseases, and equipped with adequate laboratory facilities and technicians detached from the Army medical laboratory. The plan proved efficient and was greatly expedited by the availability of penicillin for the treatment of syphilis. This made is possible to return all patients treated for syphilis to their organizations within 10 days or less.

The necessary followup was operated by a central syphilis register set up in the Office of the Chief Surgeon, European theater, where the soldier's syphilis register was filed as soon as treatment was completed. The followup was accomplished by letters to the commanding officer of the patient's organization requesting the desired observations at the appropriate time.

The Subcommittee on Venereal Diseases made further recommendations at its 23d meeting on 29 June 1944 for the use of penicillin in the treatment of syphilis by the Army. These provided for the treatment of all soldiers with early and latent syphilis with 2.4 million units of penicillin according to the scheme advised to the oversea theaters. The necessity for frequent followup of patients who were treated for early syphilis was emphasized, and it was pointed out that knowledge concerning the action of penicillin in neurosyphilis was so imperfect as to prevent any advice on its use in such cases. TB MED 106, 11 October 1944, developed in detail the general principles contained in the committee's recommendations.

As the war ended, TB MED 198, 20 August 1945, defined the criteria for the diagnosis of syphilis, restated the advice to treat early and latent

[37] Letter, Maj. Gen. Norman T. Kirk, The Surgeon General, to Commanding Generals, all Theaters of Operations, attention of Chief Surgeon, 24 May 1944, subject: Penicillin Treatment of Primary and Secondary Syphilis.

syphilis with 2.4 million units of penicillin in 7.5 days, defined the details of the necessary posttreatment followup, and advised that all patients with any manifestation of late syphilis, including, of course, neurosyphilis, be transferred to the appropriate neurosyphilis center. Like its companion TB MED 196 on gonorrhea, dated 20 August 1945, this bulletin on the management of syphilis represented the best information available at the time for the proper management of early and latent syphilis among Army personnel, but events which could not be foreseen at the time of its preparation necessitated important changes in the dosage schedules recommended.

At its 24th meeting on 23 February 1945, the Subcommittee on Venereal Diseases recognized that there were several fractions of the substance known as penicillin, that none of these fractions was available commercially, and that the constitution of commercially available penicillin was not known. It made recommendations for extending the assay supervision of commercial penicillin and most importantly made provision for investigation of the chemical and biological properties of the several known fractions. By the following spring, a great deal of information had been assembled and published by Moore, the highlights of which were (1) that the substance known as penicillin was made up of at least four chemically individual fractions which in the American nomenclature were known as G, F, X, and K, (2) that originally the commercially supplied penicillin was largely made up of penicillin G, (3) that with the substitution of *Penicillium chrysogenum* Q–176 for *Penicillium notatum* in the manufacture of penicillin the commercially available preparations contained an unknown, certainly large (the average was estimated at about 50 percent) amount of fraction K, and (4) that fraction K while exceedingly active in vitro was apparently in some way denatured by the animal or human body to become comparatively inert and therapeutically ineffective when injected. As these facts were brought out, the manufacturers of penicillin immediately took steps to convert to the production of a crude penicillin consisting largely of fraction G and eventually to the production of crystalline penicillin G on a commercial scale. This took time, however, since so large and complicated an industry cannot convert itself overnight. For the protection of the soldier patient, Change 1 to TB MED 198 was published on 21 November 1946. This change directed (1) that patients with seronegative primary syphilis be given 6 million units of penicillin in 60 doses of 100,000 units each at 3-hour intervals for 7½ days, (2) that those with seropositive primary, secondary, and latent syphilis be given 8 million units in 80 consecutive intramuscular injections of 100,000 units at 3-hour intervals for 10 days, and (3) that the re-treatment of failures be by the 8-million-unit schedule with the addition of 10 doses each of 60 mg. of Mapharsen given twice weekly and five weekly intramuscular injections each of 0.2 gm. of bismuth subsalicylate suspension in oil. Failures after this combined penicillin, Mapharsen, and bismuth schedule were to be treated

by the 26-week Mapharsen and bismuth system outlined in Circular Letter No. 74, 25 July 1942.

Comparison between Circular Letter No. 18, 10 March 1941, and TB MED 198, 20 August 1945, affords a number of interesting contrasts. To the criteria for diagnosis has been added the concept of the biological false-positive serological test for syphilis which was first introduced to the Army in Circular Letter No. 93, Office of the Surgeon General, 30 April 1943; methods of treatment are totally different, but the most interesting change is in the concept of proper posttreatment followup. Under the scheme of treatment recommended by Circular Letter No. 18, the patient who came under treatment with early syphilis and pursued the treatment faithfully should have reached and maintained a negative serological test for some time before the treatment was ended. With rapid treatment with penicillin, this is not the case, and TB MED 198 goes to some pains to explain the interpretation of the titered serological test in the posttreatment followup.

Neurosyphilis.—Prior to 1944, the Army had made no special provision for the care of patients with neurosyphilis and the various forms of late syphilis. Patients suffering from these maladies, unless by chance they fell into the hands of someone professionally qualified to individualize their management, were treated, if at all, by whatever scheme was in vogue at the time for the treatment of early syphilis. While cardiovascular syphilis and the other forms of late syphilis, other than of the central nervous system, were numerically unimportant, examination, by increasing numbers of medical officers, of the cerebrospinal fluid of every patient with syphilis was revealing a substantial number with asymptomatic neurosyphilis. As this situation became recognized, a special committee met in Washington at the request of The Surgeon General on 8 March 1944 to consider the problem of the professional management of neurosyphilis in the U.S. Army.[38] In due time, TB MED 48, 31 May 1944, was published creating a number of neurosyphilis centers in named general hospitals in the continental United States and setting forth standards for diagnosis and treatment. The plan was to staff each of the hospitals with one or more medical officers with special training in the management of neurosyphilis and other forms of late syphilis, and although these hospitals were designated as neurosyphilis centers it was tacitly understood at the time, and later formally stated in TB MED 198, that all problem cases of syphilis would be referred to them.

The provisions of TB MED 198 were largely administrative but the basic principles leading to uniformity of diagnosis in the various centers

[38] Present at the meeting were Drs. Moore and Stokes from the Subcommittee on Venereal Diseases; General Morgan, Lt. Col. Thomas H. Sternberg, MC, Maj. (later Lt. Col.) Charles R. Rein, MC, Maj. (later Lt. Col.) William H. Everts, MC, Major Dyar, and Maj. (later Lt. Col.) Paul G. Reque, MC, from the U.S. Army; Comdr. W. H. Schwartz, MC, and Lt. H. P. Rowe, MC, from the U.S. Navy; Drs. Lewis H. Weed, E. Cowles Andrus, T. R. Forbes, Philip S. Owen, and Maj. Gen. James C. Magee, USA (Ret.), from the National Research Council; Maj. Georges Leclerc, MC, and Surgeon Lieut.-Comdr. R. G. Struthers, MC, Canadian Liaison Officers; and the following invited conferees: Drs. Harry C. Solomon, Paul A. O'Leary, Evan W. Thomas, and Arthur G. Schoch.

were defined and general recommendations for classification and treatment were made. These were extended by a series of three articles[39] which were published in the *Bulletin of the U.S. Army Medical Department* where they served as authoritative but unofficial guides.

The specific recommendations of TB MED 48 for treatment were:

1. A trial of routine metal chemotherapy on a duty status for 6 months for all patients with early syphilis or syphilis of unknown duration and Groups I (minimal) and II (intermediate) changes in the cerebrospinal fluid.

2. The same scheme for patients with late syphilis and Group I changes.

3. The immediate induction of fever (preferably by tertian malaria for whites and Northern Negroes, and by quartan malaria for Southern Negroes) in those in the first two groups in whom 6 months of metal chemotherapy had occasioned no improvement in the cerebrospinal fluid, and in all patients with Group III (maximal) changes in the cerebrospinal fluid, those with late asymptomatic neurosyphilis and Group II changes, and all patients with symptomatic neurosyphilis except those with acute syphilitic meningitis or predominantly vascular lesions.

Great stress was laid upon the necessity for both frequent and long continued followup examinations of all patients treated for neurosyphilis, and detailed directions for accomplishing this were laid down regardless of whether the man stayed in the Army or was separated.

On 13 November 1945, Change 3 to TB MED 48 advised that all patients with neurosyphilis should be treated with penicillin. The recommended dose was 3.6 million units given in 120 injections of 30,000 units each in the usual manner.

The patients who qualified for a trial of metal chemotherapy alone under the previous regimen were to be returned to duty after completion of the treatment with penicillin, followed with clinical examination and retest of the cerebrospinal fluid at 3 and 6 months after treatment, and returned for reevaluation if either examination gave abnormal results 6 months after treatment was completed.

The same group of patients as previously were considered candidates for fever therapy, and the suggestion was made that the first doses of the prescribed 3.6 million units of penicillin be given at the time of the first febrile paroxysm.

Records.—The old practice of recording treatment of syphilis, as outlined in Circulars Nos. 2 and 3, 13 December 1910 and 3 June 1911, respectively, Office of the Surgeon General, was continued in more or less its orig-

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[39] (1) O'Leary, P. A., Moore, J. E., Solomon, H. C., Stokes, J. H., and Thomas, E.: Asymptomatic Neurosyphilis. Bull. U.S. Army M. Dept. 80: 46 51, September 1944. (2) Solomon, H. C., Moore, J. E., O'Leary, P. A., Stokes, J. H., and Thomas, E.: Symptomatic Neurosyphilis; A Clinical Survey. Bull. U.S. Army M. Dept. 81: 55-64, October 1944. (3) Solomon, H. C., Moore, J. E., O'Leary, P. A., Stokes, J. H., and Thomas, E. W.: The Treatment of Neurosyphilis. Bull. U.S. Army M. Dept. 82: 66 76, November 1944.

inal form until after World War I, during which it had proved to be unnecessarily laborious and to serve no useful purpose. By this time numerous individual medical officers had created their own record systems and their ideas were consolidated, eventually to produce WD MD Form 78, The Syphilis Register. This was authorized by War Department General Orders No. 6, 13 February 1923, and incorporated in AR 40–235 on 30 December 1924.

This form with relatively minor changes (the last was necessitated by the introduction of penicillin) has been employed since its first introduction. The form is opened at the time of the original diagnosis of syphilis, contains all of the relevant information concerning both the infection and the general physical condition of the patient, provides space for recording treatment, reactions, the results of laboratory tests, and progress notes and is closed at the completion of treatment and a specified period of observation. Upon completion, the record was transmitted to the Venereal Disease Control Division, Preventive Medicine Service, Office of the Surgeon General, where it was reviewed and, if found acceptable, filed for future record.[40]

During the period in which the treatment for syphilis was prolonged, this record facilitated continuity of treatment of the patient which might all be carried out in the same place or by the same medical officers. During the first part of World War II, however, because of the rapid and secret troop movements, it frequently became impossible for the syphilis register to keep up with the patient. Several different methods of accomplishing this were explored, including a brief trial of having the syphilis register transmitted with the service record of the soldier concerned, but none proved to be entirely satisfactory.

In an effort to obviate this difficulty, there was inaugurated at Fort Bragg, in 1941,[41] an individual record of treatment patterned after the similar form supplied to seamen under the auspices of the then functioning Health Organization of the League of Nations. This served to give the patient a pocket record of treatment which provided adequate information for any medical officer into whose hands he might fall. The proper functioning of this accessory form, of course, depended on the willingness of the patient to report for treatment before his syphilis register caught up with him, but experience showed that on the average the form substantially reduced the number and duration of lapses from treatment. Similar forms were introduced in the European theater in 1942 and in the Mediterranean Theater of Operations, U.S. Army, in 1943. Still another but again similar form (WD MD Form 78a) which had been authorized by The Surgeon General in October 1943 was made available by TB MED 3, 11 January 1944.

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[40] By an agreement between The Surgeons General of the Army and the Public Health Service and the Chief Medical Officer of the Veterans' Administration, the syphilis registers from World War II were filed with the Veterans' Administration to arrange for men in certain categories, especially those treated for neurosyphilis, to be followed through the Public Health Service.

There were also other exceptions to this standard procedure; for example, the Central Syphilis Registry used in the European theater.

[41] Annual Report, Office of the Surgeon, Fort Bragg, N.C., 1941.

After the introduction of rapid treatment methods, all done under the continuing control of one small group, a form of this type was no longer required for assisting in continuity of treatment, but it may continue to serve a useful purpose in facilitating posttreatment followup.

THE MINOR VENEREAL DISEASES

Aside from chancroid, which became troublesome in certain areas, the lesser venereal diseases (lymphogranuloma venereum and granuloma inguinale) were of little numerical importance during World War II. Although these three types of venereal diseases were less common than gonorrhea or syphilis, the period of disability often produced by each of them was potentially great enough to vest them with a certain degree of military importance. The earlier deliberations of the Subcommittee on Venereal Diseases which had led to the suggestions upon which Circular Letters Nos. 18 and 74 were based, included considerations of the lesser venereal diseases, and these circulars laid down methods of diagnosis and treatment of these conditions. Later, TB MED 157, dated April 1945, with Change 1, dated 17 December 1946, brought up to date the accepted practices in the diagnosis and treatment of the minor venereal diseases.[42]

Chancroid.—Up to the end of World War II, the diagnosis of chancroid was one of exclusion and therefore essentially unsatisfactory. Circular Letters Nos. 18 and 74 and TB MED 157 emphasized the necessity of excluding syphilis, both by dark-field examination and by serological followup, and that this must be done even if the diagnosis of chancroid can be proved bacteriologically in order to exclude a mixed infection. At the time of the first directive, the bacteriology of *Hemophilus ducreyi* was so unsatisfactory that Circular Letter No. 18 reads, as follows: "Laboratory tests for the absolute diagnosis of chancroid (Ito-Reenstierna skin test or the staining or cultural isolation of the Ducrey bacillus) are not recomended." In TB MED 157, considerable advance in the bacteriology of the causative organism is illustrated in the following statement: "The diagnosis of chancroid may be aided by the laboratory examination of stained smears from the lesion, or by culture of pus from the lesion or the bubo." This reflects a growing interest in the bacteriology of chancroid and the fact that the experts have developed methods for more accurately staining and for culturing the Ducrey bacillus which are satisfactory in their hands. The complete omission of the

[42] TB MED 157 was based on the recommendations of a special committee which convened on 25 January 1945 at the request of The Surgeon General. Present at the meeting were Dr. Moore, Subcommittee on Venereal Diseases; Lt. Col. (later Col.) Harrison J. Shull, MC, Colonel Sternberg, and Major Rein, representatives of The Surgeon General; Dr. Paul D. Rosahn, Technical Aide to the Committee on Medical Research, Office of Scientific Research and Development; and the following conferees: Dr. Arthur W. Grace, Long Island College of Medicine, Brooklyn, N.Y.; Dr. Geoffrey W. Rake, Squibb Institute for Medical Research, New Brunswick, N.J.; Dr. Katherine H. Anderson, Vanderbilt University School of Medicine, Nashville, Tenn.; Dr. Franco Mortara, New York University College of Medicine, New York, N.Y.; and Dr. Robert B. Greenblatt, U.S. Public Health Service.

Ito-Reenstierna or other similar skin test from this latest directive is apparently a reflection of the growing doubt of the value of skin tests of this type in general.

In contrast to the unsatisfactory state surrounding the diagnosis of chancroid, treatment with the sulfonamide drugs was eminently satisfactory. Circular Letter No. 18 recommended sulfanilamide in the dose of 33 gm. given over a period of 14 days and local treatment with powdered sulfanilamide after primary syphilis had been excluded by a series of at least three dark-field examinations of material from the lesions. Surgical procedures, such as circumcision or dorsal slit, "* * * should be resorted to only on the basis of sound clinical judgment." Incision of the fluctuant bubo was allowed but not advised.

The changes between the recommendations just cited and those contained in TB MED 157 are worth comment. The more recent recommendations were to treat systemically with sulfadiazine in a dose of 1 gm., four times daily, for 5 to 7 days; no local treatment except soap and water; aspiration of the fluctuant bubo with a 16-gage needle if necessary but, "the bubo should never be incised," and regarding other surgical procedures "circumcision or dorsal slit is undesirable and is rarely necessary."

As indicated earlier, chancroid became exceedingly prevalent and consequently troublesome in certain areas. This was especially true in the Philippines,[43] at the end of the war, and earlier in North Africa[44] and the China-Burma-India theater.[45] Recommendation by special investigators of the problem in the Philippines, however, dealt largely with control and preventive measures. In no theaters in which chancroid was troublesome was there advance in therapy greater than that reported in TB MED 157.

Lymphogranuloma venereum.—Fortunately, this disease was of low incidence both in the continental United States and in the theaters of operations. In the latter, the disease occurred almost entirely in small sporadic outbreaks clearly suggesting a single focus of infection. The same three directives (p. 430) deal with diagnosis and treatment.

Between the first and the last, there was essentially no change in the diagnostic criteria laid down. TB MED 157 explains that the diagnosis is based upon collateral consideration of the results of the Frei test, the clinical picture, epidemiological information, and the exclusion of other causes of inguinal adenopathy. It is emphasized that a positive Frei test is not in itself adequate reason for making the diagnosis of lymphogranuloma vener-

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43 Letter, Dr. Joseph Earle Moore, Consultant to The Surgeon General, U.S. Army, and Lt. Col. Thomas H. Sternberg, MC, Director, Venereal Disease Control Division, Office of the Surgeon General, U.S. Army, to The Adjutant General, U.S. Army, 6 June 1945, subject: Venereal Disease in the U.S. Army in the Philippine Islands, and Recommendations for Their Control.

44 Annual Report, Preventive Medicine Division, Office of the Surgeon, North African Theater of Operations, 1943.

45 Letter, 1st Lt. M. A. Bouton, MC, VD Control Officer, Office of the Theater Surgeon, Rear Echelon, Headquarters, U.S. Army Forces, China, Burma and India, to Commanding General, Rear Echelon, Headquarters, U.S. Army Forces, China, Burma, and India, 8 Apr. 1943, subject: Venereal Disease Situation in the C.B.I. Theater.

eum in the absence of the typical clinical picture, but it is suggested that a negative Frei test in the presence of a suggestive clinical picture is of some value in excluding the diagnosis.

In the treatment of lymphogranuloma venereum, conservatism is advised. TB MED 157 recommends aspiration of fluctuant nodes where necessary but avoidance of radical surgical procedures; chemotherapy with sulfadiazine in doses of 3 gm. daily for 21 days; and the utmost conservatism in management of rectal stricture when it occurs. Perirectal abscess and fistulo-in-ano may be dealt with radically in the hope of gaining surgical cure. The use of Frei antigen intravenously, which was previously touched upon lightly in Circular Letter No. 18, was not even mentioned.

Granuloma inguinale.—This disease was completely unimportant from the military standpoint but was included in the various directives (p. 430) for the sake of completeness. TB MED 157 suggests that the diagnosis of the condition can be made by a competent observer on the basis of morphology alone but points out the obvious desirability of demonstrating Donovan's bodies in smears from the lesions.

Fuadin (stibophen) was recommended as the drug of choice. This is given intramuscularly by a rather complicated dosage schedule, is commonly well tolerated, and is therapeutically effective in the majority of instances. Where there was no response to Fuadin, tartar emetic was recommended. This is given intravenously also on a rather complicated dosage schedule. It was further recommended that if secondary infection was present, penicillin be used in doses of 10,000 units intramuscularly every 3 hours for a total of 400,000 units. With the exception of this addition of penicillin for secondary infection, there were no other advances in the treatment of this condition during World War II.

Miscellaneous.—The more strictly urologic conditions which are sometimes grouped with the venereal diseases (venereal warts, gangrenous balanitis, and so on) need not be considered here, but the role of scabies as a venereal disease must be mentioned.

In the early winter of 1942, the Senior Consultant in Dermatology, Office of the Chief Surgeon, European theater, had noted that the incidence of scabies severe enough to require hospitalization in the European theater was greatly in excess of the frequency of the disease among troops in the United States. A determined campaign was instituted to educate unit medical officers in the early diagnosis and proper treatment of the disease and to provide them with benzyl benzoate for its treatment.

The incidence of the disease continued to increase and the following simple facts led to an inference that the disease was venereal in origin. Troops arriving from the Zone of Interior were free from the disease; the disease was exceedingly common among the British, especially the civilians; and the pattern of distribution of the individual cases made soldier-to-soldier spread most unlikely. From this obvious inference, a comprehensive study

of the matter was initiated based on the same type of interview by the same interviewers used in the contact investigation of gonorrhea and syphilis, and the study resulted in the conclusion that at least 90 percent of scabies among U.S. soldiers in the European theater was venereal in origin.[46] This thesis, incidentally, was amply verified in the experiences of our troops in Germany after V–E Day. There the incidence of scabies made a meteoric rise, exactly paralleling the increase in the incidence of the venereal diseases.[47]

INDUCTION OF INDIVIDUALS WITH VENEREAL DISEASE

In the early period of mobilization, persons known to have venereal disease were rejected for military service. This policy resulted in the accumulation of a large backlog consisting mainly of men rejected because they had syphilis. It was the practice, at the time, to defer men with gonorrhea and chancroid only until they became asymptomatic and then to refer them for induction. By 1942, this reservoir of manpower had grown to tremendous proportions, the manpower shortage was becoming acute, and the Army felt that its medical facilities and training program were sufficiently advanced to undertake the additional burden of inducting men with syphilis. In the fall of that year, plans were initiated to provide in certain selected posts, camps, and stations additional treatment facilities with a total capacity of 6,510 beds for the management of inductees with syphilis and to a much lesser extent the other venereal diseases. The plan was placed in operation in December 1942 by directives from The Adjutant General[48] and was functioning smoothly by March 1943.

The inductees with syphilis were hospitalized in specially provided barrack-type hospitals which were staffed by officers especially trained in the diagnosis and treatment of the venereal diseases. Some of these medical officers had been recruited from civilian life but most had been given a short intensive course at the Institute for the Control of Syphilis at the University of Pennsylvania, Philadelphia, Pa., under the auspices of the U.S. Army.

As a result of this program, 200,000 individuals with venereal disease were inducted into the Army through December 1945. Of these, nearly 170,000 were syphilitics.[49] The treatment which they received followed the current directives for the management of the venereal diseases occurring after induction and require no special comment.

One administrative problem was greatly expedited by a directive, in June 1943,[50] authorizing preinduction hospitalization for the examination of the cerebrospinal fluid of all those found to have a positive serological test for

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46 See footnotes 26, p. 420.

47 Quarterly Report, Preventive Medicine Division, Office of the Chief Surgeon, U.S. Forces in the European Theater, 1 Apr. to 30 June 1946.

48 Radiograms, The Adjutant General, to all Service Commands, 7 and 10 Dec. 1942.

49 Karpinos, B. D.: Venereal Disease Among Inductees. Bull. U.S. Army M. Dept. 8: 806–820, October 1948.

50 Letter, The Adjutant General, to all Service Commands, 9 June 1943, subject: Induction of Individuals With Positive Serology for Syphilis.

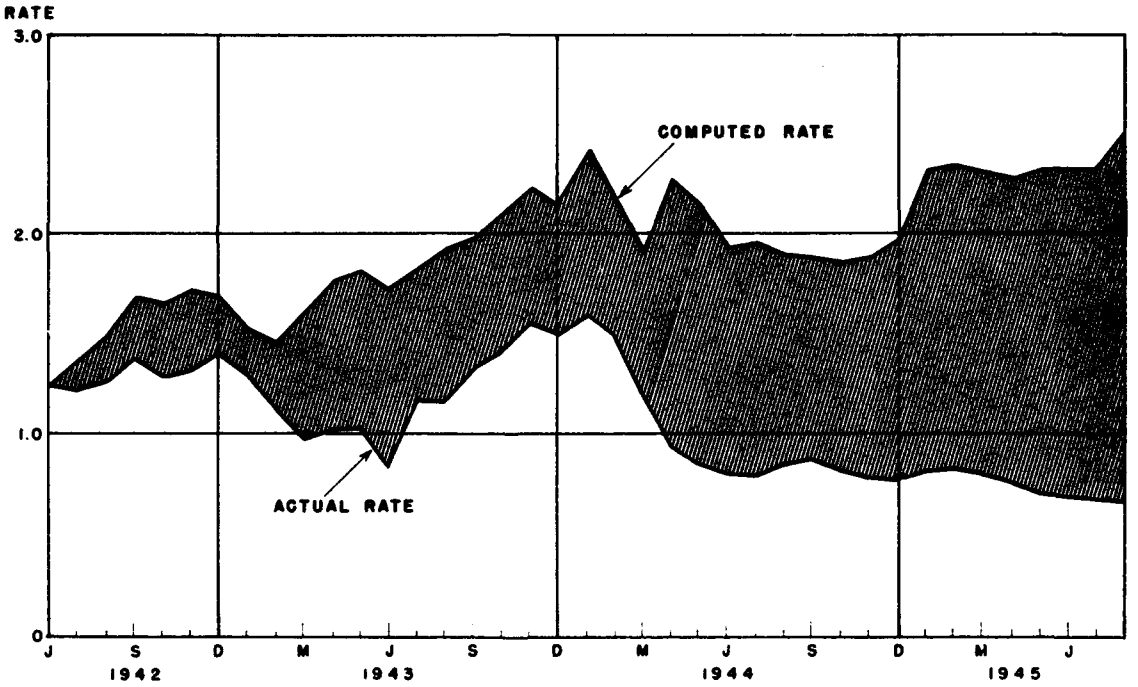
syphilis. This made possible the preinduction rejection of registrants with neurosyphilis, thereby avoiding the laborious process of boarding for a certificate of disability for discharge of the 15 to 20 percent of the men with syphilis who would be found to have an abnormal cerebrospinal fluid at the first examination.

THE RESULTS

The extremely energetic venereal disease control program which was sponsored by the Army throughout the war was effective in minimizing the number of venereal infections. In spite of these preventive activities, however, gonorrhea and syphilis continued to be among the important disease

CHART 22.—*A comparison of computed and actual rates*[1] *reflecting savings attributed to improved treatment of venereal disease, Army in the United States, June 1942 to August 1945*

[Rate expressed as average daily noneffectiveness per 1,000 average strength]



[1] Rates pertain to all cases of venereal disease, including those cases existing prior to service. For the computed rate it is assumed that the length of treatment required in June 1942 had not changed.

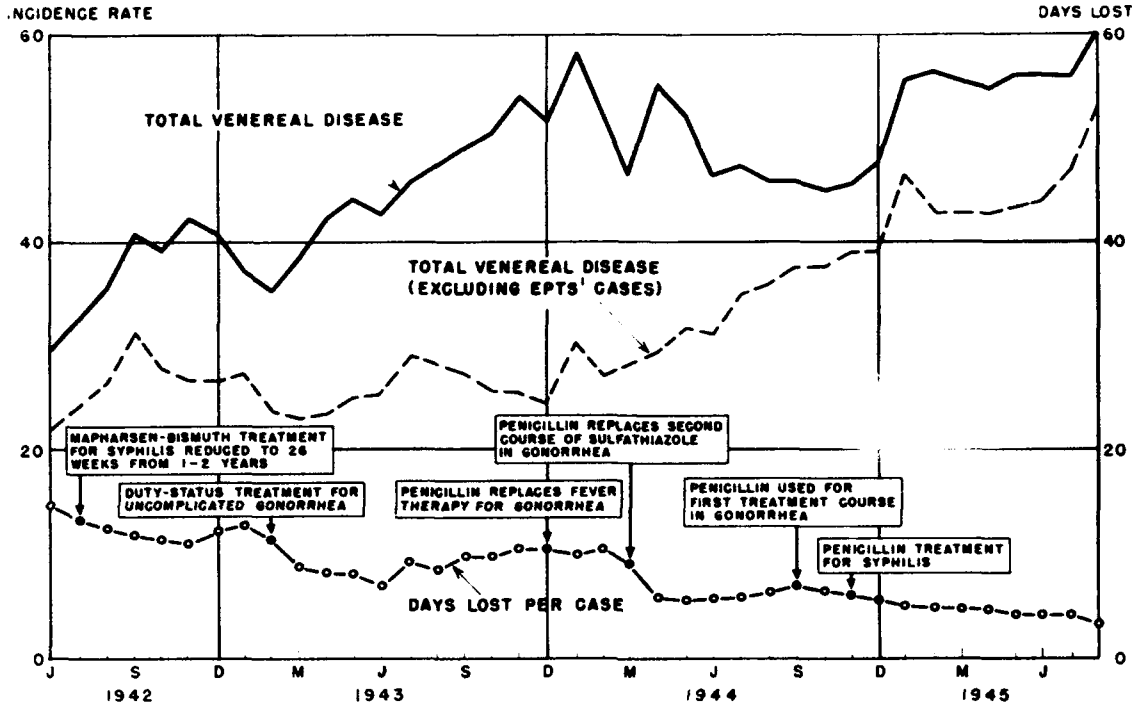
problems.[51] The yeoman's task of reducing to the minimum the number of days lost from duty because of these infections remained for the therapist who may well be proud of the accomplishment which he can report.

The reduction in the noneffective rate and changes in therapy, incidence, and duration of treatment of venereal disease in the U.S. Army in the con-

[51] Medical Department, United States Army. Preventive Medicine in World War II. Volume V. Communicable Diseases Transmitted Through Contact or By Unknown Means. Washington: U.S. Government Printing Office, 1960.

CHART 23.—*Changes in therapy, incidence, and duration of treatment of venereal disease, Army in the United States, June 1942 to August 1945*

[Incidence rate expressed as number of cases per annum per 1,000 average strength. Duration of treatment in average number of days lost per case]



[1] Existing prior to service.

tinental United States are shown in charts 22 and 23. If the length of treatment required in June 1942 had been maintained without change, the venereal disease noneffective rate for the continental United States would have been 2.0 per 1,000 per day in December 1944 and 2.5 per 1,000 per day by August 1945. As it was, in spite of the mounting venereal disease rate which skyrocketed after V-E Day, in December 1944 the noneffective rate was less than 1 per 1,000 per day and was only 0.66 per 1,000 per day in August 1945.

CHAPTER XIII

Fort Bragg Fever

Worth B. Daniels, M.D.

The recognition of Fort Bragg fever as a specific new disease entity and the ultimate proof of its etiology is a contribution of the U.S. Army Medical Department to the science of medicine. The disease was described by Army clinicians, studied by Army medical personnel with the assistance of Army-consigned consultants, transmitted to animals by an Army research worker, and finally proved as to etiology by an Army veterinarian and others working at the Medical Department Professional Service Schools, Army Medical Center, Washington, D.C.

The story of Fort Bragg fever indicates, too, the superior opportunities which were available to military medical personnel for clinical research. Larger groups of patients with the same disease are more often available for study in military installations than in civilian institutions. It is doubtful whether this disease would have been recognized as an entity had the outbreak occurred in an urban civilian community; there, each patient might have been cared for by a different physician and treated in a different hospital, whereas, on an Army post *all* were *concentrated* in one hospital under the care of a closely knit medical service.

RECOGNITION OF A NEW DISEASE

Late in July and early in August 1942, an unusual febrile illness occurred in a group of soldiers at Fort Bragg, N.C.[1] It shortly became apparent not only that these men had identical symptoms but also that they all came from a few organizations quartered near one another in a limited area of the reservation. Between 29 July and 11 September, 40 patients with this illness were admitted to the hospital. The history was one of relatively sudden onset characterized by malaise, mild general aching, lumbar pain, severe frontal headaches, and postorbital pain. On the first or second day of symptoms, mild respiratory manifestations consisting of coryza, sore throat, pain and soreness in the chest, and cough occurred in 30 percent of the patients. The respiratory symptoms were not persistent and were never suggestive of primary respiratory involvement such as is seen in influenza. In about one-fourth of the cases, nausea and vomiting occurred, rarely accompanied by abdominal pain. Shaking chills or chilliness and fever developed. The fever was consistently spiking and frequently showed two or more peaks each

[1] Daniels, W. B., and Grennan, H. A.: Pretibial Fever; An Obscure Disease. J.A.M.A. 122: 361-365, 5 June 1943.

day. Recurrent chills often accompanied the elevations. During the periods of temperature evelation, severe accentuation of the frontal and postorbital aching was experienced, but during the periods of lower temperature, the patients felt relatively well. The fever persisted for 2 to 8 days—averaging 5.4 days—with maximum elevations ranging from 99.8° to 105.6° F. In five patients, a transient evelation of temperature, sometimes as high as 101.4° F., occurred from 2 to 7 days after the original febrile period. Stiffness of the neck accompanied headache in three patients, but examination of the cerebrospinal fluid revealed it to be normal; there was no noticeable relief of headache following lumbar puncture. Adenopathy was not remarkable. A firm spleen was palpable early in the disease in 95 percent of the patients. Splenomegaly persisted in some patients for as little as 5 days: in others, there was still noticeable enlargement after 2 weeks.

The most distinctive feature of the disease, however, was the appearance of an unusual rash on or about the fourth day of illness. In 60 percent (24) of the patients, this was bilaterally symmetrical and limited in distribution to the pretibial areas; in an additional 20 percent (8 patients), the pretibial areas were the primary site of the rash, and a few lesions were scattered elsewhere. Two patients had splotchy, generalized cutaneous manifestations including the anterior surface of both legs. One had a single lesion on the hand. In five cases, typical in all other respects, no rash was observed. Individual lesions consisted of an erythematous localized blush of irregular outline with ill-defined borders fading into the surrounding skin. These were often from 2 to 5 cm. in their largest diameter, gradually coalescing with adjacent lesions. The lesions were raised, warmer than the surrounding skin, and sometimes slightly tender to touch. In some patients, the lesions vaguely resembled erythema nodosum. In two patients, the rash became diffusely distributed over the entire body, and in a few it appeared urticarial. Following the generalized type of rash there was a residual pigmentation which persisted for about 2 weeks. None of the lesions were purpuric. In most instances, the cutaneous manifestations lasted 2 days, but they persisted longer in a few patients. Figures 57 and 58 illustrate the pretibial and the generalized forms of the rash.

Biopsies of cutaneous lesions were performed in six typical cases. They showed diffuse edema and a slight to moderate perivascular infiltration with small round cells and macrophages. It is clear that drugs played no part in the development of this rash because only one patient had received sulfonamide therapy and no other patient received any drug except acetylsalicyclic acid and codeine. Leukopenia was noted sufficiently often to constitute a typical feature; it was present, in all except five patients, at some time during the acute illness. It developed most often between the third and the fifth day of illness. At the termination of the febrile period, the leukocytes again rose to normal, and in 14 patients a slight leukocytosis occurred. The number of leukocytes ranged from 2,800 to 14,000 per cubic millimeter. Dif-



FIGURE 57.—Erythematous skin lesions over the pretibial regions.

ferential counts usually showed no deviation from normal, although in a few cases a moderate relative lymphocytosis was present.

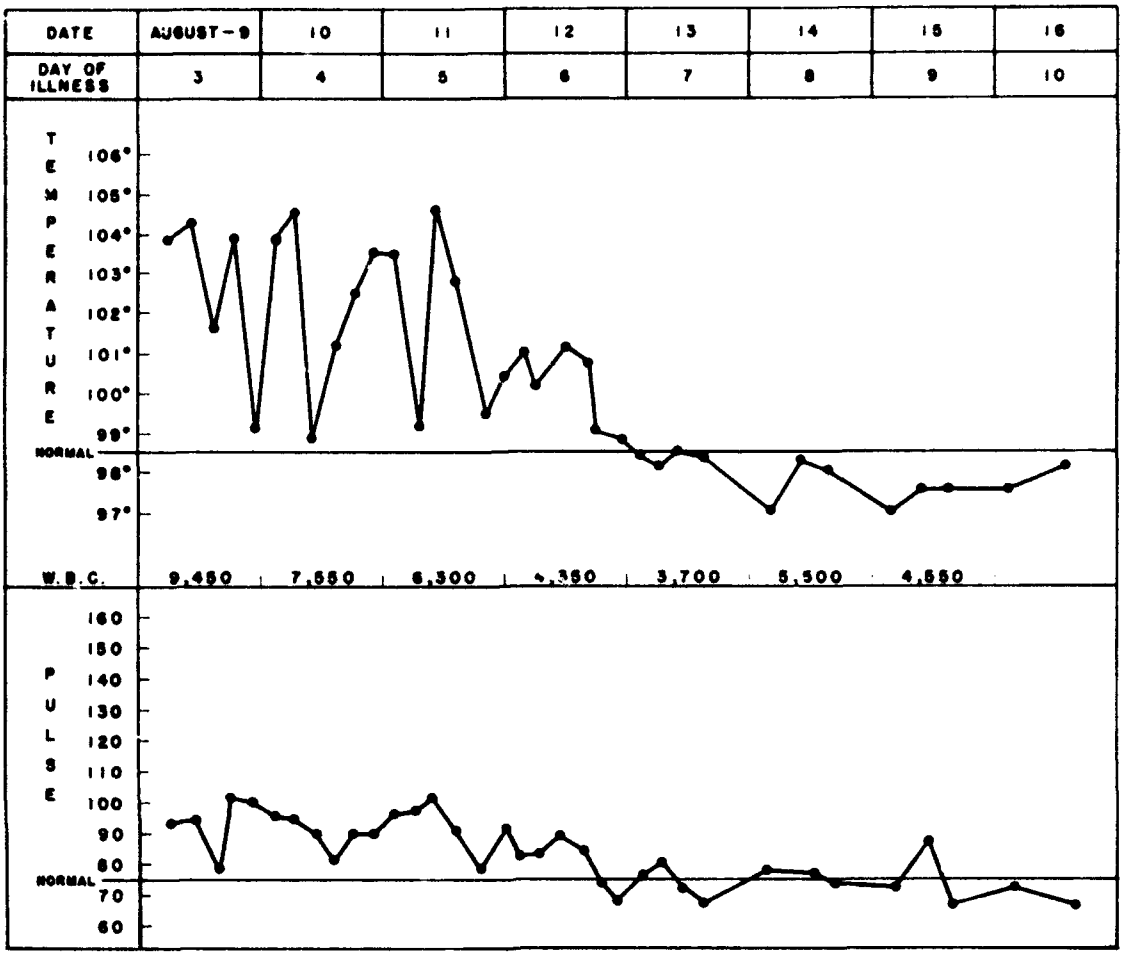
Cultures of the blood showed no growth. Agglutinations for *Proteus* OX-19, *Brucella melitensis*, the typhoid-paratyphoid group, and heterophile antibodies were negative. No patient had been in an area where coccidioidomycosis was endemic. Skin tests using coccidioidin antigen were negative in two patients after their recovery. Roentgenograms of the chest were made in many patients, but none showed any abnormality.

At the termination of the fever, the patients rapidly returned to their original healthy state. There was no postfebrile depletion or depression, and there were no complications.

CASE REPORTS

Case 1.—A white soldier, aged 25, admitted to the hospital on 7 August 1942, complained of fever and headache. He had been well until 2 days previously, when he felt feverish and chilly. Severe frontal headache, postorbital pain, and severe backache developed. The next day he felt slightly better, but on the day of admission the symptoms were all accentuated. The temperature was 101° F., the pulse rate 90, and the respiratory rate 20; the leukocytes numbered 8,150 per cu. mm. Nothing unusual was found on physical examination. On the fifth day of the disease, the spleen was firm and easily palpable. Over the pretibial surfaces of both legs, irregular, erythematous lesions were noted; these were faintly tender, warm to touch, and very slightly raised (fig. 57). The patient's temperature was swinging in character and ranged from 99.8° to 104.4° F. without a corresponding rapidity of pulse. The leukocytes numbered 4,900

CHART 24.—*Temperature, pulse, and leukocyte count of patient*



per cu. mm., with 65 percent polymorphonuclear cells. On the seventh day of illness, the rash had entirely disappeared, the temperature was normal, and the patient felt well. The spleen was still palpable at discharge from the hospital.

Case 2.—A white soldier, aged 21, admitted to the hospital on 9 August 1942—the third day of disease—had as initial symptoms frontal headache and pain in the feet and legs which later involved various joints. At the onset there was nausea without vomiting. Shaking chills had occurred on two occasions in the 36 hours prior to admission. Physical examination revealed nasal congestion, pharyngitis, signs of generalized bronchitis, a temperature of 104° F., a pulse rate of 92, and a respiratory rate of 20 (chart 24). The leukocytes numbered 9,150 per cu. mm. Two hours after admission a rash appeared on the trunk, neck, and extremities. This consisted of discrete, brilliantly erythematous, slightly raised, warm plaques varying in size from 2 to 8 cm. in their largest diameter. The rash was generalized (fig. 58) and, as in the other cases, the anterior aspects of both legs were involved. During the next few days the temperature ranged from 99° to 104.6° F., with very little acceleration of the pulse. The spleen became palpable. The rash remained erythematous for 3 days, faded gradually, and left a definite purplish pigmentation that diminished during the succeeding 2 weeks. The leukocytes were reduced to 4,350 on the sixth day and to 3,700 per cu. mm. on the seventh day, with no abnormality in the differential count. Convalescence was uneventful.



FIGURE 58. Generalized form of skin eruption.

DIFFERENTIAL DIAGNOSIS

A number of different diseases were considered in differential diagnosis. In the early cases, influenza was suspected, but the transient character and mildness of the respiratory symptoms, persistence of fever, presence of a firm palpable spleen, and the unusual rash eliminated this possibility. Endemic typhus seemed to be excluded by the short duration of the illness, by the entirely different type of rash, and by the consistently negative Weil-Felix reactions with OX 19 at different periods of the illness. Rocky Mountain spotted fever was similarly dismissed from consideration. There was no history of bites by ticks in this group. When these patients were studied, Bullis fever[2] had not yet been described, although cases were being recognized in Texas. Again, absence of bites by ticks and difference in symptomatology indicated that the cases here described were not the same as those seen at Camp Bullis, Tex. In no cases did adenopathy or the characteristic hematological changes of infectious mononucleosis develop. The duration of the disease, negative cultures of blood and stool, and negative agglutination re-

[2] Woodland, J. C., McDowell, M. M., and Richards, J. T.: Bullis Fever (Lone Star Fever, Tick Fever): An Endemic Disease Observed at Brooke General Hospital, Fort Sam Houston, Texas. J.A.M.A. 122: 1156-1160, 24 Aug. 1943.

actions eliminated the typhoid-paratyphoid group. The parasites of malaria and relapsing fever were sought, but not found. Dengue was at first thought to be the probable diagnosis. However, as new cases were observed, certain prominent features of that disease were consistently absent. No patient had a "camel back" type of fever curve or any postfebrile depletion or depression. The usual vector of dengue, *Aedes aegypti*, was not found in the vicinity. It would be unusual for an outbreak of dengue to be limited to such a small group. The type and the distribution of the rash were not similar to that seen in dengue. Other denguelike diseases were considered; however, the clinical features of this disease showed definite dissimilarity to these in one or more important respects. Search of the literature did not reveal a description of a clinical entity into which this group of cases would fit.

EPIDEMIOLOGICAL ASPECTS

The organizations from which these soldiers came were quartered in the northern third of the populated area of the reservation, near a small stream and its tributaries. Other areas of the post furnished no patients ill with this disease; therefore, local environmental factors were thought to be of etiological importance. There was no single locality off the reservation to which these men went during the month previous to illness, and they had no common meeting place on the reservation. Some of the men had done no swimming, while others swam in several different ponds. Although there was no swimming place common to all, more men swam in "McFadgen's Pond" than in any other place—on or off the reservation.

The factors responsible for the outbreak could not be determined. The medical inspector of the post made a search for insect vectors that might be suspected. Bedbugs, stableflies, chiggers, ticks, and horseflies were found but for various reasons were considered unlikely vectors.

During the period of this outbreak, the population of mosquitoes on the post was very low, but various members of the *Culex* species were found with *Culex quinquefasciatus* appearing most frequently. This mosquito had been disproved as a carrier of dengue. No representative of the dengue vector, *A. aegypti*, was found, but *Aedes atlanticus*, *Aedes canadensis*, and *Aedes vexans* were. Their presence was thought to be of doubtful importance.

After a decrease in the number of admissions to the hospital in mid-August, the incidence of the disease again increased sharply. The clinical picture, the long period of incubation, and the leukopenia suggested that the disease was probably due to a virus. The localization of the cases in one area of the post made it seem probable that it was transmitted by an insect vector. The local medical personnel were unable to carry out studies as to etiology, so The Surgeon General, U.S. Army, was requested to send especially trained individuals to study the outbreak.

SPECIAL INVESTIGATION

On 3 September 1942, Dr. Norman H. Topping, Passed Assistant Surgeon, U.S. Public Health Service, Maj. (later Lt. Col.) Cornelius B. Philip, SnC, and Dr. John R. Paul, Professor of Preventive Medicine, Yale University School of Medicine, New Haven, Conn., and Director, Commission on Neurotropic Virus Diseases, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, arrived at Fort Bragg to study the disease. The Commission reviewed the records of the case previously studied and examined the patients remaining in the hospital. They agreed that the soldiers were ill with a disease unknown to them, but Dr. Topping remembered that an outbreak of a disease with similar features had been encountered in the town of Wrens, Ga., in 1940. This illness was locally known as Brushy Creek fever. Inquiry later brought information from Dr. Charles D. Bowdoin,[3] who had observed these patients and reported them at a later date, that about 35 cases had occurred. The clinical course and manifestations seemed to be quite identical with those at Fort Bragg. A laboratory technician who had made some of the cultures of feces was reported as having developed the disease.

The Commission began investigations in regard to the epidemiology and etiology of the disease.[4] They showed that, although only 34 patients with a rash had been considered to have this disease by medical officers of the hospital, the number of cases—in one of the regiments involved—without a rash might have exceeded those with a rash by as much as 50 percent. The Commission confirmed the fact that the disease was not spread evenly throughout the camp population; but, of the 34 cases (with a rash) diagnosed between 27 July and 19 September, 75 percent had occurred in 3 regimental units. Practically all of the cases (almost 97 percent with a rash) occurred in troops quartered in the northern third of the developed area. A canvass was made of four artillery regiments quartered in the southern section of the post, and no "missed cases" were found among 4,800 troops.

These features, plus the fact that the rate of attack was particularly high in two units, led the Commission to suspect that some local, although unrecognized, environmental feature was responsible. Particular attention was paid, therefore, to two units. In each of these, an epidemic amounting almost to an explosive outbreak had occurred. These outbreaks were separated by about 3 weeks and were limited, to some extent (in the early cases), to a single company.

These explosive epidemics became apparent when a survey of the records of illness of one unit in particular, namely, the 88th Airborne Infantry,

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[3] Bowdoin, C. D.: A New Disease Entity (?). J.M.A. Georgia 31: 437-438, 442, December 1942.

[4] Preliminary Report of the Commission for the Study of an Unidentified Disease at Fort Bragg, N.C., 3-11 Sept. 1942, by Dr. Norman H. Topping, P.A. Surgeon, U.S. Public Health Service, Maj. Cornelius B. Philip, SnC, U.S. Army, and Dr. John A. Paul, Yale University School of Medicine. Submitted to The Surgeon General, U.S. Army, 15 Oct. 1942.

revealed that there had been a sharp increase of cases of "influenza," "nasopharyngitis," or "fever of undetermined origin" in this regiment during August. Of the 33 cases of "influenza," and other diseases, which were reported in August, 9 developed a rash after they had been hospitalized and were ultimately diagnosed as having Fort Bragg fever. In 14 others, whose hospital records were available for study, the picture was compatible with that of Fort Bragg fever, although the rash was lacking.

It was concluded, therefore, that a nonexanthematous form of this disease existed and (if all forms of the disease were considered) it could appear in explosive epidemic form resulting in almost 10 percent of the personnel in a given company being infected within the period of 2 weeks. Factors responsible for this type of explosive outbreak were not determined.

Certain information about the period of incubation was obtained. Five men probably developed the disease while they were away from the post and several developed it within a few days after their return, following an absence of 10 days on maneuvers on Chesapeake Bay. If it is assumed that the disease was not spread by direct contact, the data accumulated would indicate that the incubation period was from 10 to 15 days or longer.

The Commission's entomological observations indicated that if parasitic arthropods were vectors of the disease, there were only three that were found or reported in sufficient numbers and of sufficient distribution to be considered. These were stableflies (*Stomoxys calcitrans*), mosquitoes, and chiggers (*Trombicula irritans*). These parasites had also been reported to have bitten men stationed in units in the southern part of the post, where none of the cases occurred.

As to mosquitoes, it was found that a ditched but swampy arm of Tank Creek separating the two most heavily infected units could have provided the most available source of breeding, but reports of adjacent troops and of sanitary personnel indicated insufficient incidence of mosquitoes in both July and early August to account for the outbreak. The evidence of transmission by mosquitoes was not considered strong.

Having collected and *frozen* material for further study, the Commission departed on 11 September to carry out investigations of etiology in their various laboratories.

Search for an etiological agent was carried out by members of the Commission at the National Institute of Health, U.S. Public Health Service, at the Yale University School of Medicine, and at the Medical Department Professional Service Schools.[5]

The material obtained for study consisting of blood from acutely sick patients and a variety of insects (including *Stomoxys calcitrans*) had been *frozen* and kept on Dry Ice. It was inoculated into embryonated eggs, guinea

[5] Final Report of the Commission for the Study of an Unidentified Disease at Fort Bragg, N.C., 3–11 Sept. 1942, by Dr. Norman H. Topping, P.A. Surgeon, U.S. Public Health Service, Maj. Cornelius B. Philip, SnC, U.S. Army, and Dr. John R. Paul, Yale University School of Medicine. Submitted to The Surgeon General, U.S. Army, 31 Mar. 1943.

pigs, mice, monkeys, and one chimpanzee. Human transmission experiments were tried by inoculating frozen whole blood and by allowing *A. aegypti* and *Aedes albopictus* mosquitoes previously fed on a patient ill with the disease to feed on volunteers. Each one of these attempts to transmit the disease failed. In retrospect, however, the negative findings with frozen human material were explained by an important discovery made about 2 years later, when it was shown that the causative agent of this disease is destroyed by freezing. It is small wonder, therefore, that the experiments of 1942 were unsuccessful. It was not until 1st Lt. (later Capt.) Hugh Tatlock, MC, succeeded in performing direct transmission experiments with fresh blood in guinea pigs in 1944 that the disease was successfully transmitted.

Outbreaks similar to that of 1942 occurred during the summers of 1943 [6] and 1944 [7] among soldiers quartered in the same area of the post. In 1943, a rickettsia-like organism was recovered by Tatlock [8] from three of five guinea pigs injected with fresh blood from a patient ill with the disease. Attempts were made to show that this agent was concerned in the etiology of the disease. However, subsequent studies indicated that this organism was undoubtedly of guinea pig origin and not concerned in the etiology of Fort Bragg fever.

In the summer of 1944, Tatlock injected two guinea pigs and two Syrian hamsters intraperitoneally with blood freshly drawn from a patient ill for 4 days with the disease.[9] Both guinea pigs developed fever (105° to 106° F.) 8 days after inoculation. Both guinea pigs were found dead on the 10th day. No passage was attempted from the hamsters. Serial transmission of the fever-producing agent in guinea pigs was accomplished by the intraperitoneal injection of citrated blood on the first day of fever. The incubation period was 4 to 8 days and fever persisted from 2 to 4 days. More than 70 passages produced no increase in virulence of the agent. No gross abnormalities were found in sacrificed guinea pigs. Histological sections of the liver showed areas of focal necrosis. No inclusion bodies or *Rickettsia* were seen in sections.

Tatlock found the agent capable of infecting guinea pigs, rabbits, and Syrian hamsters by both intraperitoneal and intracerebral inoculation. The disease transmitted was uniformly fatal for hamsters. Intravenous inoculation of 11-day chick embryos was accomplished. From these infected eggs, the agent was propagated by the yolk-sac route, and fresh tissue suspensions were infective for hamsters in 1 to 100,000 dilution. The agent passed a Corning fritted glass filter but failed to pass a single Seitz pad. Tissue emulsions in sterile skim milk, frozen rapidly and maintained at −70° C.,

[6] Personal observation of the author.

[7] Personal communication, J. M. Kinsman, to the author.

[8] Tatlock, H.: A Rickettsia-Like Organism Recovered From Guinea Pigs. Proc. Soc. Exper. Biol. & Med. 57: 95–99, October 1944.

[9] Tatlock, H.: Studies on a Virus From a Patient With Fort Bragg Fever (Pretibial Fever). J. Clin. Investigation 26: 287–297, March 1947.

retained viability. However, blood, whole tissues, or tissues suspended in broth lost infectivity when stored for 24 hours at 20° C., 4° C., or at −70° C. in sealed glass ampules.

Sera from five patients with Fort Bragg fever were used in protection tests. Neutralization was obtained in two patients with convalescent, but not with acute, sera. Comparable results were obtained with two sets of sera from infected guinea pigs.

By early 1945, Captain Tatlock had brought his studies to a point where he and others interested in the disease were confident that Fort Bragg fever was due to a well-characterized filtrable virus unrelated to any other known virus. At this juncture, he was ordered to Walter Reed General Hospital, Army Medical Center, for clinical duties but maintained the agent there by passages and by storage, frozen in an emulsion of milk.

During the summer months of 1945, no patients with this disease were admitted to the hospital at Fort Bragg. It is of interest that a large part of the post area in which patients had previously seemed to acquire the disease was unoccupied except for a period of "a week or two." [10]

Isolated reports appeared of single cases of Fort Bragg fever in Connecticut,[11] New York,[12] and California.[13] From the descriptions given, these patients may have had this disease, although it would seem difficult to make an absolute diagnosis in the absence of an outbreak.

ADDENDUM

In the spring of 1946, Captain Tatlock was ordered on detached service to Cincinnati, Ohio, where, through the cooperation of Dr. Albert B. Sabin and of the Longview State Hospital, he began studies in transmission among a group of patients undergoing fever therapy. He inoculated three patients intramuscularly and intracutaneously with a 10-percent suspension of infected, embryonated chick liver in saline. This material had been through 80 passages in guinea pigs and 23 passages [14] in embryonated eggs. After an incubation period of 8 to 9 days all three patients developed a short febrile illness. Successful inoculation of three other patients, using freshly defibrinated pooled blood from the previous patients, was accomplished, and a third passage was successful in seven of eight other individuals. All but one of the latter patients, after an incubation period comparable to that of the natural disease (8 to 14 days), developed fever, and the majority exhibited the clinical picture of Fort Bragg fever with rash and leukopenia. For the third passage, two patients immune to "New Guinea C" strain of dengue fever virus, two immune to the "Hawaiian" strain of virus, and two immune

[10] Personal communication, J. H. Dingle, to the author.

[11] Lipscomb, L. L., and McMahon, J. L.: Pretibial Fever. J.A.M.A. 128: 90 91, 12 May 1945.

[12] Greenfield, I.: Pretibial Fever; A New Disease Entity. Urol. & Cutan. Rev. 47: 435 436, July 1943.

[13] Personal communication, G. Cheney, to the author.

[14] See footnote 9, p. 445.

to the "Middle East-Sicilian" type of sandfly fever virus were used. All were found susceptible to the "virus" of Fort Bragg fever.

"Viremia" was demonstrated in these patients by the immediate inoculation of fresh, defibrinated blood into young hamsters. The "virus" appeared in the blood of these patients shortly before the onset of fever and disappeared rapidly thereafter.

It now appeared clear to all interested in the disease that the "virus" isolated by Tatlock from a case of Fort Bragg fever in 1944 was a new and distinct agent capable of producing the classical manifestations of the natural disease when inoculated into man.

In 1947, in New Haven, Melnick and Paul [15] inoculated four chimpanzees intracutaneously and subcutaneously, using the "virus" isolated by Captain Tatlock. These animals developed a disease similar in many respects to the experimental disease transmitted to humans by Tatlock, and subsequent bleedings showed that they had developed neutralizing antibodies. When "virus" inactivated by freezing was inoculated into five chimpanzees, no disease or neutralizing antibodies developed. Two of these animals were later given active "virus" and both developed antibodies. Two animals were studied for "viremia" during the period of fever. This was demonstrated in one of the animals by transmission to a chimpanzee and in the other by transmission to young hamsters.

During the ensuing years, the "virus" of Fort Bragg fever was maintained in several laboratories. The possibility that this agent might be a *Leptospira* was considered several times by Gochenour, Smadel, and others at the Army Medical Service Graduate School, Walter Reed Army Medical Center.[16] However, results obtained with methods then employed failed to support this idea.

Later, a large collection of leptospiral strains was assembled by this group. In the fall of 1951, Gochenour, an Army veterinarian—with Smadel and other coworkers—found that with antigens prepared from these strains convalescent and immune sera of victims of Fort Bragg fever gave a high titer of agglutinating antibodies against *Leptospira autumnalis.* With this lead, a leptospiral organism was recovered by culture from the 365th passage of the Fort Bragg agent since its original isolation. Cross-agglutination tests showed that the Fort Bragg agent was essentially indistinguishable from *Lept. autumnalis* Akiyami A, the cause of autumnal fever in Japan and other areas of the Far East. There was then no doubt that *Lept. autumnalis* was being carried in this laboratory as the "virus" of Fort Bragg fever. Obviously, it was of the utmost importance to learn whether this was a contaminant or whether it really originated from patients with the disease at Fort Bragg.

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[15] Melnick, J. L., and Paul, J. R.: Experimental Fort Bragg Fever (Pretibial Fever) in Chimpanzees. Proc. Soc. Exper. Biol. & Med. 67: 263–268, March 1948.

[16] Gochenour, W. S., Jr., Smadel, J. E., Jackson, E. B., Evans, L. B., and Yager, R. H.: Leptospiral Etiology of Fort Bragg Fever. Pub. Health Rep. 67: 811–813, August 1952.

Paired sera from Melnick and Paul's four euphoniously named chimpanzees—Rosebud, Mary Lou, Hickory, and Catawba—showed high titers of agglutinins or neutralizing antibodies against *Lept. autumnalis* in the convalescent, but none in the acute, sera. Paired sera from six of Captain Tatlock's patients infected in Cincinnati gave the same results.

Fortunately, paired sera from five of the original soldiers who had been bled by Tatlock in 1944 were still safe in the Deepfreeze. Three of these patients were found to have developed neutralizing antibodies and leptospiral agglutinins. Two who failed to develop neutralizing antibodies in Captain Tatlock's experiments also failed to agglutinate *Lept. autumnalis*.

It is of great interest that three lots of hyperimmune rabbit sera—one prepared in 1947 from the hamster line, another in 1951 from cultured *Leptospirae* of the Fort Bragg agent, and a third from cultures of *Lept. autumnalis* Akiyami A—protected hamsters against 100,000 LD_{50} of the Fort Bragg *Leptospira*.

Stored sera from 45 Fort Bragg patients ill in 1943 or 1944, though not paired, were studied. Sixteen of these gave clear-cut serological evidence of infection with Fort Bragg *Leptospira*.

Fort Bragg fever then is caused by a member of the *Lept. autumnalis* group. No member of this group was previously known to exist in the United States. This disease takes its place with Weil's disease, swineherd's disease, canicola fever, and other leptospiral diseases and is a contribution of Army medical investigation to medicine.

CHAPTER XIV

Statistics of Malaria

Fred H. Mowrey, M.D.

Malaria, one of the world's greatest causes of morbidity, has played a dominant role in many military campaigns, although not so devastatingly as the pestilential diseases of typhus, plague, the dysenteries, and smallpox.

HISTORICAL NOTE

Malaria played a vital part in Caesar's campaigns during the Roman civil wars. Malaria was the savior of Rome from the Germans on many occasions. Celli [1] writes: "The Queen of the World suffered much at the hands of these Barbarians, but, in her dethronement, she found ample revenge. For in the swamps around Rome there lurked swarms of mosquitoes eager for fresh healthy blood, and they it was that now attacked the foreign invaders. These Northern warriors, who were forced to spend the summer within or outside Rome, died, or lingered on for years weakened by daily fever, and this happened over and over again for centuries with a terrifying regularity. The various German troops made their departures more in the manner of a funeral procession than in a victor's triumph." Celli referring to Otto I in 964 writes, "The Emperor, however, celebrated the Nativity of St. John (June 24) and the Feast of the Holy Apostles (June 29) and turned homewards from the Roman Land. But he was overcome by a fate more unhappy than he could ever have looked for, for in his army there broke out so great and deadly a pestilence that almost all died, and those who still kept their health only dared to hope to live from one evening to the next morning." In 1167, Emperor Frederick I failed to conquer Rome. "Suddenly, such a deadly fever broke out in his Army that, within seven days, almost all the princes who fought with him against the Church were unexpectedly snatched away by a miserable death." He was forced to flee leaving uncounted dead.

Malaria was ever-present during the Siege of Mantua in 1796–97. Prinzing [2] states that malaria broke out with great severity and acquired virulent forms which played a decisive role in the result.

A typical example of the effect of malaria in military campaigns occurred among British and French troops in Macedonia in 1918. Some 80 percent of 120,000 French troops were hospitalized. Over 25,000 British troops were invalided home with chronic malaria, and more than 2 million

1 Celli, Angelo: The History of Malaria in the Roman Campagna. London: John Bale, Sons & Danielsson, Ltd., 1933.

2 Prinzing, Friedrich: Epidemics Resulting From Wars. Oxford: At The Clarendon Press. 1916.

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man-days were lost in the British Macedonian Army during 1918 because of malaria.[3]

Malaria also has been a problem to the U.S. Army. There are no available statistics on malaria prior to 1818, but we know it was prevalent before then. "As early as 1776 the Continental Congress ordered the Medical Committee to forward 300 pounds of Peruvian bark to the Southern Department for the use of troops."[4]

During the War Between the States, one-half of the white troops and four-fifths of the Negro troops in the Northern Armies contracted malaria annually. There were 10,063 deaths due to malaria. In addition, more than 1,000 Confederate troops died of malaria in Northern prisons. The incidence of malaria during the U.S. Civil War, in Northern troops, per 1,000 per annum, is shown in the following tabulation:[5]

Fiscal year	*White troops*	*Negro troops*
1861–62	390.7	(1)
1862–63	428.3	(1)
1863–64	535.9	811.6
1864–65	496.6	703.2
1865–66	829.5	920.6

[1] No Negro troop strength.

During the Spanish-American War, there were 90,461 admissions for malaria during the calendar year 1898, with 349 deaths. The annual admission rate was 611.78 per 1,000. A rate of 1,924.78 per 1,000 per annum occurred in Cuba with a mortality rate of 14.02 per 1,000 per annum.[6] Theodore Roosevelt stated that malaria was the chief enemy in Cuba. Every officer in his regiment, except himself, was down at one time or another with malarial fever. "Though the percentage actually on the sicklist never got above twenty, there were less than fifty percent who were fit for any kind of work."[7]

In the First World War, from 1 April 1917 to 31 December 1919, there were 15,555 admissions for malaria, 36 deaths, 28 discharges for disability, and 194,529 man-days lost. Most of the malaria occurred among troops engaged in training in facilities located in endemic malarious areas in the United States. Only 950 admissions for malaria occurred in Europe.[8]

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[3] Wenyon, C. M., Anderson, A. G., McLay, K., Hele, T. S., and Waterston, J.: Malaria in Macedonia, 1915–1919. J. Roy. Army M. Corps 37: 81–108, August 1921.

[4] Blanton, W. B.: Medicine in Virginia in the Eighteenth Century. Richmond, Va.: W. Byrd Press, 1931.

[5] Medical and Surgical History of the War of the Rebellion. Medical History. Washington: Government Printing Office, 1888, pt. III, vol. I.

[6] Annual Report of The Surgeon General, U.S. Army. Washington: Government Printing Office, fiscal year, 1900.

[7] Major, Ralph H.: Fatal Partners: War and Disease. Garden City, N.Y.: Doubleday, Doran & Co., Inc., 1941, p. 195.

[8] The Medical Department of the United States Army in the World War. Washington: U.S. Government Printing Office, 1928, vol. IX, p. 512.

The incidence of malaria among U.S. troops was of little significance following World War I, occurring chiefly among troops stationed in Panama, Puerto Rico, and the Philippine Islands. The incidence for the entire Army during 1941 was 4.74 per 1,000 per annum.

WORLD WAR II

The disease became, however, a problem of serious importance during World War II, when U.S. Army troops campaigned in highly malarious areas in many parts of the world. Never before had the Medical Department been called upon to combat a problem of such magnitude. It is indeed a tribute to the preventive measures adopted that the menace of malaria did not more seriously interfere with military operations. However, these sanitary measures were not immediately available to combat troops in such areas as Guadalcanal, New Guinea, China, Burma, India, North Africa, Sicily, Italy, and elsewhere. Accordingly, malaria exacted its toll in morbidity and man-days lost.

Malaria assumed a dominant role in many Pacific areas—Green Island, Emirau, Bougainville, Vella Lavella, Suaba, Efate, Espíritu Santo, Guadalcanal, Tulagi-Florida, Russell Islands, Munda, and the Treasury Islands—seriously depleting combat effectiveness and increasing the workload of the Medical Department. This was best illustrated in Guadalcanal where there were 10,206 primary cases of malaria among U.S. Army troops during March-December 1943:[9]

1943[1]	*Number of primary cases*
March	845
April	3,374
May	1,926
June	1,117
July	1,123
August	608
September	566
October	315
November	177
December	155
Total	10,206

[1] Data are not available for primary cases occurring in January and February.

The 1st Marine Division ceased to be an effective combat unit for many months owing to the hospitalization for malaria of approximately 80 percent of the command.[10] Four out of five units had to be removed from combat for rehabilitation. The Americal Division was transferred from New Cale-

[9] Essential Technical Medical Data, South Pacific Base Command, for March 1945. Inclosure 13-4, unnumbered table entitled "Primary Cases of Malaria, Army, Guadalcanal, 1942-44."

[10] Essential Technical Medical Data, Southwest Pacific Area, for January 1944.

donia to Guadalcanal during November and December 1942. Owing to the exigencies of combat and failure to appreciate the problem, few, if any, antimalarial measures were taken. The number of cases of malaria rapidly increased, weekly rates as high as 2,500 per 1,000 per annum being reported. The division had to be transferred to Fiji in March 1943 for rehabilitation. Mass therapy of the division was undertaken between April and June, when all medication was discontinued. The hospitalization rate promptly rose to 4,220 in August. It was still 2,948 in late October when suppressive therapy with Atabrine (quinacrine hydrochloride) was reinstituted, with a consequent drop to 80 by late December 1943.[11]

The 25th Infantry Division engaged in combat on Guadalcanal in January 1943. This division also failed to take proper antimalarial measures. As a consequence, the malaria rate rose to 2,385 per 1,000 per annum during the last week of April. This division was transferred to New Zealand in December 1943 for rehabilitation, and thence to New Caledonia in February 1944 for reorganization. It is estimated that approximately 46 percent of the division had one or more attacks of malaria during 1943.

The 43d Infantry Division entered Guadalcanal in March 1943 and subsequently participated in the Russell Islands and New Georgia campaigns. This division required rehabilitation in New Zealand during February and March 1944. In order to determine the amount of seeding in the division, a small control group was taken off Atabrine. The malaria rate for this group rose to 2,000 per 1,000 per annum; whereas the rate for the remainder of the division, which continued on Atabrine suppression, did not exceed 236 per 1,000 per annum.

Malaria was a great problem in the Southwest Pacific Area, 47,663 attacks occurring during 1943 alone. Sixty-seven percent of the 32d Infantry Division had malaria during the 10-month period following their withdrawal from New Guinea. The effectiveness of malarial control was demonstrated in the Milne Bay area of New Guinea where the rate was 3,308 in January 1943. Following the institution of control measures, the rate dropped to 100 by May and to only 30.72 by January 1944.[12]

There were 9,160 cases of malaria in the China-Burma-India theater during 1943, with nearly 115,000 man-days lost. Of the first 2,400 patients admitted to the 20th General Hospital, located near Ledo in Assam, 73 percent had malaria. At one time, 55 percent of the beds were occupied by patients with malaria.[13] The effect on troops of exposure to the endemic disease is illustrated by 92 men of the 900th Airborne Engineer Company who traveled from Ledo to Tagap. En route, 54 were hospitalized with malaria; out

[11] Essential Technical Medical Data, South Pacific Area, for April 1944.
[12] Essential Technical Medical Data, Southwest Pacific Area, for May 1944.
[13] Essential Technical Medical Data, China-Burma-India Theater, for August 1943.

of the 38 who reached Tagap, 20 had malaria on arrival.[14] An epidemic of malaria occurred at the 1306th Air Force Base Unit, Air Transport Command, located in Karachi, India, in 1944. There were no cases during August, but the rate rose rapidly to 1,202.3 per 1,000 per annum during the first 2 weeks of October. The rate dropped to 148 during the first 2 weeks of November following the institution of malaria control methods.[15]

Malaria was a serious problem to North African theater forces. It was prevalent in the areas of Rabat and Port Lyautey in Morocco, the Constantine area in Algeria, the Tunis-Bizerte-Ferryville area in Tunisia, Catania in Sicily, Corsica, Sardinia, Salerno, Paestum, and the Pontine Marshes in Italy. There were 69,000 cases during 1943–44 with 944,000 man-days lost. One and two-tenths percent of patients with malaria were evacuated to the United States.[16] During the Sicilian campaign, the Seventh U.S. and British Eighth Armies lost, from malaria alone, the equivalent of the fighting effectiveness of two infantry divisions. In fact, there were more losses due to malaria than there were battle casualties; the Seventh U.S. Army reported 9,892 cases of malaria and 8,375 battle casualties and the British Eighth Army reported 11,590 and approximately 9,000, respectively.[17]

It is interesting to note that nearly all of the total malaria cases (32,796) in the European theater were imported by troops who had originally served in the North African theater. There were 4,806 cases of malaria among U.S. troops stationed in England before D-day 1944.

Altogether, during the period 1942–45, there were 492,299 cases of malaria, 410,727 of these occurring overseas; the total attack rate per 1,000 average strength per annum was 19.43 and was highest during 1943 and 1944 (table 53). Data on the noneffective rates for malaria are not presently available, but from 8 to 9 million man-days were estimated to have been lost because of malaria during 1942–45, at an average daily noneffective rate of 1 per 1,000 average strength; the estimated rate based on the average duration multiplied by the number of admissions and readmissions is 0.94.

Of the 492,299 cases of primary malaria occurring during 1942–45 with a rate of 19.43 per 1,000 average strength (table 54), the greatest number of cases occurred in the Southwest Pacific followed by the Central and South Pacific, the Mediterranean, and China-Burma-India theaters. The highest incidence rate, 98.46, occurred in the China-Burma-India theater.

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[14] Recorded Interview. Office of the Surgeon General, 20 Apr. 1944, subject: Report of Medical Department Activities in China-Burma-India by Maj. John H. Grindlay, MC, Chief, Surgical Service, 20th General Hospital, India.

[15] Annual Report, Surgeon, India-China Division Air Transport Command, 1944.

[16] Golz, Harold H.: Human Malaria in the North African and Mediterranean Theaters of Operations, U.S. Army. [Official record]

[17] Essential Technical Medical Data. North African Theater of Operations, U.S. Army, for October 1943.

TABLE 53.—*Total attack rate*[1] *for malaria in the U.S. Army, by area,*[2] *type of plasmodium, and year, 1942–45*

[Preliminary data based on sample tabulations of individual medical records]

[Rate expressed as number of cases per annum per 1,000 average strength]

Type of plasmodium	1942–45		1942		1943		1944		1945	
	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate
	Continental United States									
Vivax (tertian) malaria	74,197	5.02	1,387	0.52	4,625	0.89	27,045	6.81	41,140	13.80
Falciparum (estivo-autumnal) malaria	761	.05	186	.07	245	.05	175	.04	155	.05
Malaria, mixed type	248	.02	23	.01	20	.00	130	.03	75	.03
Malariae (quartan) malaria	294	.02	34	.01	45	.01	120	.03	95	.03
Malaria, unclassified and other	6,072	.41	427	.16	1,300	.25	2,055	.52	2,290	.77
Total	81,572	5.51	2,057	0.77	6,235	1.20	29,525	7.43	43,755	14.68
	Overseas									
Vivax (tertian) malaria	267,079	25.33	10,048	17.15	87,596	51.90	102,765	26.90	66,670	14.98
Falciparum (estivo-autumnal) malaria	50,519	4.79	4,295	7.33	28,054	16.62	12,750	3.34	5,420	1.22
Malaria, mixed type	3,196	.30	193	.33	1,173	.69	1,020	.27	810	.18
Malariae (quartan) malaria	1,583	.15	88	.15	640	.38	680	.18	175	.04
Malaria, unclassified and other	88,350	8.38	6,586	11.24	51,169	30.32	21,415	5.61	9,180	2.06
Total	410,727	38.96	21,210	36.20	168,632	99.91	138,630	36.30	82,255	18.48
	Total Army									
Vivax (tertian) malaria	341,276	13.47	11,435	3.53	92,221	13.42	129,810	16.66	107,810	14.51
Falciparum (estivo-autumnal) malaria	51,280	2.02	4,481	1.38	28,299	4.12	12,925	1.66	5,575	.75
Malaria, mixed type	3,444	.14	216	.07	1,193	.17	1,150	.15	885	.12
Malariae (quartan) malaria	1,877	.07	122	.04	685	.10	800	.10	270	.04
Malaria, unclassified and other	94,422	3.73	7,013	2.16	52,469	7.64	23,470	3.01	11,470	1.54
Total	492,299	19.43	23,267	7.18	174,867	25.45	168,155	21.58	126,010	16.95

[1] Includes admissions for the first time for malaria, readmissions, and admissions for other causes, but in which malaria existed concurrently or developed subsequently.

[2] Area of admission to medical treatment, but not necessarily the area in which the disease was acquired.

TYPES OF MALARIA

Malaria due to *Plasmodium vivax*, *Plasmodium falciparum*, and *Plasmodium malariae* occurred in all theaters. Malaria caused by *P. vivax* had the highest incidence rates in the China-Burma-India theater, the Southwest Pacific and the Central and South Pacific Areas. The majority of the cases in the United States were of this type. The highest incidence rates due to *P. falciparum* occurred in the Middle East and the China-Burma-India the-

TABLE 54.—*Attack rates* [1] *of malaria, all forms in the U.S. Army, by area and year, 1942–45*

[Preliminary data based on sample tabulations of individual medical records]

[Rate expressed as number of cases per annum per 1,000 average strength]

Area [2]	1942–45		1942		1943		1944		1945	
	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate
Continental United States	81,572	5.51	2,057	0.77	6,235	1.20	29,525	7.43	43,755	14.93
Overseas:										
Europe	32,796	7.81	69	0.83	662	2.48	17,585	10.49	14,480	6.66
Mediterranean [3]	80,532	52.60	735	32.06	33,232	72.76	38,830	59.78	7,735	19.25
Middle East	10,715	80.53	746	123.39	6,669	125.73	2,900	62.75	400	14.41
China-Burma-India	44,052	98.46	1,077	123.14	9,160	231.21	26,265	155.68	7,550	32.78
Southwest Pacific	124,109	78.25	4,451	62.49	47,663	250.98	33,475	62.08	38,520	49.03
Central and South Pacific	95,828	66.53	2,934	19.44	65,489	224.62	17,275	39.38	10,130	18.12
North America [4]	200	.41	71	.71	89	.46	25	.19	15	.22
Latin America	17,891	47.05	11,042	108.34	4,874	40.34	1,245	14.51	730	10.19
Total overseas [5]	410,727	38.96	21,210	36.20	168,632	99.91	138,630	36.30	82,255	18.48
Total Army	492,299	19.43	23,267	7.18	174,867	25.45	168,155	21.58	126,010	16.95

[1] Consists of new admissions and readmissions for malaria as well as admissions for other causes, but in which malaria existed concurrently or developed subsequently.

[2] Area of admission to medical treatment, but not necessarily the area in which the disease was acquired.

[3] Includes North Africa.

[4] Includes Alaska and Iceland.

[5] Includes cases on board transports.

ater. Ninety-seven percent of malaria acquired in Liberia was due to *P. falciparum*.[18] *P. malariae* was found chiefly in the Mediterranean, the Southwest Pacific, China-Burma-India, and the Central and South Pacific Areas. The incidence rate of clinical *P. malariae* infections without classification was highest in China-Burma-India, the Southwest Pacific and the Central and South Pacific Areas.

P. vivax was the etiological agent in 341,276 cases; *P. falciparum*, in 51,280; *P. malariae*, in 1,877; and there were 3,444 cases with mixed type infections, or a total of about 397,000 in which plasmodia were identified. The remaining 94,442 cases were unclassified, the diagnosis being made on clinical signs and symptoms without microscopic verification. (See tables 55, 56, 57, 58, and 59.)

RELAPSE IN MALARIA

There are no accurate statistical data available on relapse rates. However, it is well known that malaria ascribed to *P. vivax* was prone to relapse under the therapeutic regimens in use during World War II. The relapse rate of malaria due to *P. falciparum* was markedly lower than that caused by *P. vivax*, although a significant number did relapse.

[18] Annual Report, U.S. Army Forces in Liberia, 1943.

TABLE 55.—*Attack rates* [1] *of* vivax (*tertian*) *malaria, in the U.S. Army, by area and year, 1942–45*

[Preliminary data based on sample tabulations of individual medical records]

[Rate expressed as number of cases per annum per 1,000 average strength]

Area [2]	1942–45		1942		1943		1944		1945	
	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate
Continental United States	74,197	5.02	1,387	0.52	4,625	0.89	27,045	6.81	41,140	13.80
Overseas:										
Europe	26,011	6.19	42	0.51	299	1.12	14,060	8.39	11,610	5.34
Mediterranean [3]	55,489	36.24	371	16.18	15,818	34.63	32,310	49.74	6,990	17.39
Middle East	2,349	17.65	95	15.71	934	17.61	1,125	24.34	195	7.03
China-Burma-India	26,122	58.38	412	47.11	4,010	101.22	15,335	90.90	6,365	27.63
Southwest Pacific	83,076	52.38	884	12.41	27,902	146.92	24,215	44.91	30,075	38.28
Central and South Pacific	58,600	40.69	499	3.31	34,866	119.59	14,260	32.52	8,975	16.05
North America [4]	119	.24	48	.48	36	.19	20	.15	15	.22
Latin America	12,657	33.29	7,672	75.27	3,430	28.39	990	11.54	565	7.88
Total overseas [5]	267,079	25.33	10,048	17.15	87,596	51.90	102,765	26.90	66,670	14.98
Total Army	341,276	13.47	11,435	3.53	92,221	13.42	129,810	16.66	107,810	14.51

[1] Consists of new admissions and readmissions for malaria as well as admissions for other causes, but in which malaria existed concurrently or developed subsequently.

[2] Area of admission to medical treatment, but not necessarily the area in which the disease was acquired.

[3] Includes North Africa.

[4] Includes Alaska and Iceland.

[5] Includes cases on board transports.

TABLE 56.—*Attack rates* [1] *of* falciparum (*estivo-autumnal*) *malaria in the U.S. Army, by area and year, 1942–45*

[Preliminary data based on sample tabulations of individual medical records]

[Rate expressed as number of cases per annum per 1,000 average strength]

Area [2]	1942–45		1942		1943		1944		1945	
	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate
Continental United States	761	0.05	186	0.07	245	0.05	175	0.04	155	0.05
Overseas:										
Europe	391	0.09	5	0.06	176	0.66	135	0.08	75	0.03
Mediterranean [3]	7,446	4.86	144	6.28	6,257	13.70	965	1.49	80	.20
Middle East	7,502	56.38	568	93.95	5,299	99.90	1,515	32.78	120	4.32
China-Burma-India	8,265	18.47	280	32.01	2,265	57.17	5,250	31.12	470	2.02
Southwest Pacific	13,624	8.59	233	3.27	5,166	27.20	3,945	7.32	4,280	5.45
Central and South Pacific	8,756	6.08	248	1.64	7,628	26.16	730	1.66	150	.27
North America [4]	29	.06	5	.05	24	.12	----------	0	----------	0
Latin America	4,326	11.38	2,803	27.50	1,173	9.71	200	2.33	150	2.09
Total overseas [5]	50,519	4.79	4,295	7.33	28,054	16.62	12,750	3.34	5,420	1.22
Total Army	51,280	2.02	4,481	1.38	28,299	4.12	12,925	1.66	5,575	0.75

[1] Consists of new admissions and readmissions for malaria as well as admissions for other causes, but in which malaria existed concurrently or developed subsequently.

[2] Area of admission to medical treatment, but not necessarily the area in which the disease was acquired.

[3] Includes North Africa.

[4] Includes Alaska and Iceland.

[5] Includes cases on board transports.

TABLE 57.—*Attack rates* [1] *of* malariae (*quartan*) *malaria, in the U.S. Army, by area and year, 1942–45*

[Preliminary data based on sample tabulations of individual medical records]

[Rate expressed as number of cases per annum per 1,000 average strength]

Area [2]	1942–45		1942		1943		1944		1945	
	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate
Continental United States	294	0.02	34	0.01	45	0.01	120	0.03	95	0.03
Overseas:										
Europe	192	0.05	1	0.01	21	0.08	140	0.08	30	0.01
Mediterranean [3]	473	.31	3	.13	330	.72	135	.21	5	.01
Middle East	125	.94	3	.50	32	.60	90	1.95	---	0
China-Burma-India	241	.54	9	1.03	77	1.94	145	.86	10	.04
Southwest Pacific	274	.17	4	.06	60	.32	115	.21	95	.12
Central and South Pacific	146	.10	7	.05	84	.29	45	.10	10	.02
North America [4]	2	.00	2	.02	---	0	---	0	---	0
Latin America	102	.27	59	.58	33	.27	5	.06	5	.07
Total overseas [5]	1,583	0.15	88	0.15	640	0.38	680	0.18	175	0.04
Total Army	1,877	0.07	122	0.04	685	0.10	800	0.10	270	0.04

[1] Consists of new admissions and readmissions for malaria as well as admissions for other causes, but in which malaria existed concurrently or developed subsequently.

[2] Area of admission to medical treatment, but not necessarily the area in which the disease was acquired.

[3] Includes North Africa.

[4] Includes Alaska and Iceland.

[5] Includes cases on board transports.

TABLE 58.—*Attack rates* [1] *of malaria, mixed type, in the U.S. Army, by area and year, 1942–45*

[Preliminary data based on sample tabulations of individual medical records]

[Rate expressed as number of cases per annum per 1,000 average strength]

Area [2]	1942–45		1942		1943		1944		1945	
	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate
Continental United States	248	0.02	23	0.01	20	0.00	130	0.03	75	0.03
Overseas:										
Europe	67	0.02	1	0.01	6	0.02	40	0.02	20	0.01
Mediterranean [3]	540	.35	2	.09	213	.47	250	.38	75	.19
Middle East	67	.50	4	.66	18	.34	25	.54	20	.72
China-Burma-India	427	.95	20	2.29	112	2.83	225	1.33	70	.30
Southwest Pacific	1,168	.74	26	.37	267	1.41	315	.58	560	.71
Central and South Pacific	724	.50	13	.09	521	1.79	150	.34	40	.07
North America [4]	1	.00	---	0	1	.01	---	0	---	0
Latin America	161	.42	127	1.25	29	.24	5	.06	---	0
Total overseas [5]	3,196	0.30	193	0.33	1,173	0.69	1,020	0.27	810	0.18
Total Army	3,444	0.14	216	0.07	1,193	0.17	1,150	0.15	885	0.12

[1] Consists of new admissions and readmissions for malaria as well as admissions for other causes, but in which malaria existed concurrently or developed subsequently.

[2] Area of admission to medical treatment, but not necessarily the area in which the disease was acquired.

[3] Includes North Africa.

[4] Includes Alaska and Iceland.

[5] Includes cases on board transports.

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TABLE 59.—*Attack rates* [1] *of malaria, unclassified and other,* [2] *in the U.S. Army, by area and year, 1942–45*

[Preliminary data based on sample tabulations of individual medical records]

[Rate expressed as number of cases per annum per 1,000 average strength]

Area [3]	1942–45		1942		1943		1944		1945	
	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate
Continental United States	6,072	0.41	427	0.16	1,300	0.25	2,055	0.52	2,290	0.77
Overseas:										
Europe	6,135	1.46	20	0.24	160	0.60	3,210	1.92	2,745	1.26
Mediterranean [4]	16,584	10.83	215	9.38	10,614	23.24	5,170	9.96	585	1.46
Middle East	672	5.05	76	12.57	386	7.28	145	3.14	65	2.34
China-Burma-India	8,997	20.11	356	40.70	2,696	68.05	5,310	31.47	635	2.76
Southwest Pacific	25,967	16.37	3,304	46.38	14,268	75.13	4,885	9.06	3,510	4.47
Central and South Pacific	27,602	19.16	2,167	14.35	22,390	76.79	2,090	4.76	955	1.71
North America [5]	49	.10	16	.16	28	.14	5	.04	----------	0
Latin America	645	1.70	381	3.74	209	1.73	45	.52	10	.14
Total overseas [6]	88,350	8.38	6,586	11.24	51,169	30.32	21,415	5.61	9,180	2.06
Total Army	94,422	3.73	7,013	2.16	52,469	7.64	23,470	3.01	11,470	1.54

[1] Consists of new admissions and readmissions for malaria as well as admissions for other causes, but in which malaria existed concurrently or developed subsequently.

[2] Other than *vivax, falciparum, malariae,* and mixed type.

[3] Area of admission to medical treatment, but not necessarily the area in which the disease was acquired.

[4] Includes North Africa.

[5] Includes Alaska and Iceland.

[6] Includes cases on board transports.

The problem of relapses can best be illustrated by citing the experience in several areas. Approximately 30 percent of the troops of the 43d, 37th, 25th, and Americal Divisions had over four attacks of malaria by June 1944.[19] Twenty percent of these relapses occurred within 2 months of the primary attack. The overall relapse rate in the China-Burma-India theater was estimated at 25 percent for *vivax* infections.[20] The 26th Field Hospital reported that approximately 60 percent of the malaria admissions were recurrences. Some of these patients had had 8, 10, and 14 previous attacks of malaria.[21] Forty percent of 11,343 cases of malaria studied in the Mediterranean theater from 1 January to 1 December 1944 were recurrent cases. The relapse rate in this theater was estimated to be from 50 to 55 percent.[22] In the Southwest Pacific Area, 392 cases of primary malaria were studied.

[19] Report, Capt. James E. T. Hopkins, MC, Surgeon, 3d Battalion Medical Detachment, 5307th Composite Unit (Provisional), 22 June 1944, subject: Preliminary Report of Physical and Mental Condition of Men and Officers of the 3d Battalion With Recommendations.

[20] Essential Technical Medical Data, China-Burma-India Theater, for June 1944.

[21] Annual Report, 26th Field Hospital, Persian Gulf Command, 1944.

[22] See footnote 16, p. 453.

Of the total, 153 cases had relapses, the first relapse occurring on an average of 50 days after the primary attack. In 49 of the 153 cases, the second relapse occurred on an average of 54 days after the first relapse. In 18 of the 49 cases, 3 or more relapses each, occurred: 14 had 3 relapses, 2 had 4 relapses, and the remaining 2 had 5 relapses.[23]

The following tabulation gives the percentage of relapses in a group of patients studied in Italy during January 1945.[24]

Number of previous attacks	*Percent*
1	39.2
2	21.4
3	21.4
4	10.7
5	5.3

Eighteen hospitals in the Mediterranean theater reported the number of relapses experienced by 3,512 recurrent cases of malaria, as follows:

Number of previous attacks	*Number of patients*	*Percent*
1	1,685	48.0
2	777	22.1
3	435	12.4
4	267	7.6
5	138	3.9
6	79	2.2
7	69	2.0
8	31	.9
9	16	.5
10	7	.2
11	8	.2
Total	3,512	100.0

DURATION OF HOSPITALIZATION

Data on the average duration of hospitalization for malaria in the entire Army were available only for the years 1942, 1943, and 1945, at the time this analysis was made.

The average stay in hospital and quarters varied from a low of 13.6 days in 1945 to a high of 22.2 days in 1943 (table 60). Malaria due to a mixed type of infection required a longer period of hospitalization than did malaria due to a single species of *Plasmodium*. It is perhaps significant that the duration of hospitalization for fever of undetermined origin was much less than that due to malaria.

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[23] Essential Technical Medical Data, Southwest Pacific Area, for July 1944.

[24] Essential Technical Medical Data, Mediterranean Theater of Operations, for February 1945.

TABLE 60.—*Average number of days in hospital and quarters for admissions and readmissions due to malaria and fever of undetermined origin, U.S. Army, 1942, 1943, and 1945*

[Preliminary data based on sample tabulations of individual medical records]

Diagnosis	1942	1943	1945
Malaria, all forms	16.6	22.2	13.6
Vivax (tertian) malaria	16.7	25.3	13.7
Falciparum (estivo-autumnal) malaria	15.6	18.6	14.0
Malariae (quartan) malaria	19.0	21.8	10.8
Malaria, mixed type	22.5	61.1	16.6
Malaria, unclassified	16.8	17.9	11.5
Fever of undetermined origin	8.1	7.5	6.9

DEATHS DUE TO MALARIA

There were 302 deaths due to malaria during the period 1942–45; 292 of these deaths occurred among oversea admissions; of this total, 157 deaths occurred in Pacific areas: 113 deaths recorded for the Southwest Pacific and 44 deaths for the Central and South Pacific Areas, table 61. The annual rates per 100,000 average strength were highest in China-Burma-India followed by the Middle East, Southwest Pacific, and Latin American areas. The rates varied from year to year, the highest, 20.19 per 100,000 average strength, occurring in the China-Burma-India theater during 1943.

The majority of deaths, 125, and the highest annual rate per 100,000 average strength, 0.49, were due to *P. falciparum*. *P. vivax* accounted for 68

TABLE 61.—*Deaths due to malaria, all forms,*[1] *in the U.S. Army, by area of admission and year of death, 1942–45*

[Preliminary data based on tabulations of individual medical records]
[Rate expressed as number of deaths per annum per 100,000 average strength]

Area	1942-45		1942		1943		1944		1945	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Continental United States	10	0.07	1	0.04	3	0.06	2	0.05	4	0.13
Overseas:										
Europe	5	0.12	----	0	----	0	4	0.24	1	0.05
Mediterranean [2]	57	3.72	3	13.09	40	8.76	13	2.00	1	.25
Middle East	12	9.02	1	16.54	5	9.43	3	6.49	3	10.81
China-Burma-India	40	8.94	1	11.43	8	20.19	25	14.82	6	2.60
Southwest Pacific	113	7.12	5	7.02	23	12.11	31	5.75	54	6.87
Central and South Pacific	44	3.05	2	1.32	28	9.60	9	2.05	5	.89
North America [3]	----	0	----	0	----	0	----	0	----	0
Latin America	18	4.73	12	11.77	5	4.14	1	1.17	----	0
Total overseas [4]	292	2.77	24	4.10	110	6.52	87	2.28	71	1.60
Total Army	302	1.19	25	0.77	113	1.64	89	1.14	75	1.01

[1] There were no deaths due to *malariae* (quartan) malaria.
[2] Includes North Africa.
[3] Includes Alaska and Iceland.
[4] Includes one death each year on transports, 1943, 1944, and 1945, respectively.

deaths and mixed infections for 6. No deaths were caused by *P. malariae.* There were 103 deaths due to unclassified malaria. (See tables 62, 63, 64, and 65.)

TABLE 62.—*Deaths due to* vivax *(tertian) malaria, in the U.S. Army, by area of admission and year of death, 1942–45*

[Preliminary data based on tabulations of individual medical records]
[Rate expressed as number of deaths per annum per 100,000 average strength]

Area	1942–45		1942		1943		1944		1945	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Continental United States	5	0.04	----------	0	1	0.02	2	0.05	2	0.07
Overseas:										
Europe	4	0.10	----------	0	----------	0	3	0.18	1	0.05
Mediterranean [1]	14	.91	1	4.36	6	1.31	6	.92	1	.25
Middle East	----------	0	----------	0	----------	0	----------	0	----------	0
China-Burma-India	5	1.12	----------	0	----------	0	4	2.37	1	.43
Southwest Pacific	25	1.58	1	1.40	8	4.21	4	.74	12	1.53
Central and South Pacific	10	.69	----------	0	8	2.74	----------	0	2	.36
North America [2]	----------	0	----------	0	----------	0	----------	0	----------	0
Latin America	5	1.32	3	2.94	2	1.66	----------	0	----------	0
Total overseas	63	0.60	5	0.85	24	1.42	17	0.45	17	0.38
Total Army	68	0.27	5	0.15	25	0.36	19	0.24	19	0.26

[1] Includes North Africa.
[2] Includes Alaska and Iceland.

TABLE 63.—*Deaths due to* falciparum *(estivo-autumnal) malaria, in the U.S. Army, by area of admission and year of death, 1942–45*

[Preliminary data based on tabulations of individual medical records]
[Rate expressed as number of deaths per annum per 100,000 average strength]

Area	1942–45		1942		1943		1944		1945	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Continental United States	3	0.02	1	0.04	1	0.02	----------	0	1	0.03
Overseas:										
Europe	----------	0	----------	0	----------	0	----------	0	----------	0
Mediterranean [1]	27	1.76	2	8.73	22	4.82	3	.46	----------	0
Middle East	11	8.27	1	16.54	5	9.43	2	4.33	3	10.81
China-India-Burma	20	4.46	----------	0	6	15.14	12	7.12	2	.87
Southwest Pacific	43	2.71	----------	0	5	2.63	11	2.04	27	3.43
Central and South Pacific	8	.56	----------	0	5	1.71	2	.46	1	.18
North America [2]	----------	0	----------	0	----------	0	----------	0	----------	0
Latin America	10	2.62	7	6.87	2	1.66	1	1.17	----------	0
Total overseas [3]	122	1.15	10	1.71	46	2.73	32	0.83	34	0.77
Total Army	125	0.49	11	0.34	47	0.69	32	0.41	35	0.46

[1] Includes North Africa.
[2] Includes Alaska and Iceland.
[3] Includes one death each year on transports, 1943, 1944, and 1945, respectively.

TABLE 64.—*Deaths due to malaria, mixed type, in the U.S. Army, by area of admission and year of death, 1942–45*

[Preliminary data based on tabulations of individual medical records]

[Rate expressed as number of deaths per annum per 100,000 average strength]

Area	1942–45		1942		1943		1944		1945	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Continental United States	----------	0	----------	0	----------	0	----------	0	----------	0
Overseas:										
China-Burma-India	2	0.45	----------	0	----------	0	1	0.59	1	0.43
Southwest Pacific	2	.13	----------	0	1	.53	----------	0	1	.13
Central and South Pacific	2	.14	----------	0	----------	0	2	.46	----------	0
Other theaters	----------	0	----------	0	----------	0	----------	0	----------	0
Total overseas	6	0.06	----------	0	1	0.06	3	0.08	2	0.04
Total Army	6	0.02	----------	0	1	0.01	3	0.04	2	0.03

TABLE 65.—*Deaths due to malaria, unclassified and other,*[1] *in the U.S. Army, by area of admission and year of death, 1942–45*

[Preliminary data based on tabulations of individual medical records]

[Rate expressed as number of deaths per annum per 100,000 average strength]

Area	1942–45		1942		1943		1944		1945	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Continental United States	2	0.01	----------	0	1	0.02	----------	0	1	0.03
Overseas:										
Europe	1	0.02	----------	0	----------	0	1	0.06	----------	0
Mediterranean [2]	16	1.05	----------	0	12	2.63	4	.62	----------	0
Middle East	1	.75	----------	0	----------	0	1	2.16	----------	0
China-Burma-India	13	2.91	1	11.43	2	5.05	8	4.74	2	.87
Southwest Pacific	43	2.70	4	5.62	9	4.74	16	2.97	14	1.78
Central and South Pacific	24	1.66	2	1.32	15	5.15	5	1.13	2	.35
North America [3]	----------	0	----------	0	----------	0	----------	0	----------	0
Latin America	3	.79	2	1.96	1	.82	----------	0	----------	0
Total overseas	101	0.96	9	1.54	39	2.31	35	0.92	18	0.41
Total Army	103	0.41	9	0.28	40	0.58	35	0.45	19	0.26

[1] Other than *vivax*, *falciparum*, *malariae*, and mixed type.

[2] Includes North Africa.

[3] Includes Alaska and Iceland.

SUMMARY

The role of malaria in military campaigns was reemphasized once more during World War II. The magnitude of the problem is illustrated by a brief presentation of statistical data giving the incidence of malaria, the types of malaria, the relapse problem, and the number of deaths due to malaria. It is indeed a tribute to the Medical Department of the U.S. Army, that the menace of malaria did not more seriously interfere with military operations.

CHAPTER XV

The Suppression of Malaria

Benjamin M. Baker, M.D.

From the onset of World War II, it was recognized that tropical diseases could interfere seriously with military operations. Previous military histories [1] had adequately delineated this problem. What was not known, however, was the extent to which troops might be incapacitated by malaria under the conditions of modern warfare in the Tropics. Planners could not count on the opportunity to rid hostile shores or vast hinterlands of endemic malaria by elimination of mosquito breeding. In the long run, the effectiveness of U.S. troops in many parts of the world depended principally on the suppression of clinical malaria by the use of new drugs and the development of techniques of chemotherapy.

Most medical officers arrived on the scene with little knowledge of malaria and even less practical experience. At first, the only sources of information were the few available textbooks and the directives prepared by The Surgeon General, U.S. Army. One of the directives, Circular Letter No. 56, Office of the Surgeon General, dated 9 June 1941 recommended the following regarding chemical prophylaxis:

> The use of quinine or Atabrine for prophylaxis is not recommended as a routine procedure, as the available information indicates that these drugs do not prevent infection. However, they are of definite military value in that they do prevent the appearance of the clinical symptoms of malaria so long as they are taken, and thus they afford a means for keeping troops "on their feet" during periods of emergency in the field. When administered to troops in special situations in unsanitated endemic areas, either of the drugs may be used under the personal supervision of a responsible officer, as follows: (1) Atabrine 0.2 gm. (3 gr.) twice a week (every 3 or 4 days) or (2) Quinine sulphate 0.3 gm. (5 gr.) daily.

When in a very short time it became clear that the high malaria rates in exposed troops constituted a serious problem, the few available trained experts on malaria were enlisted to direct hurried efforts to bring about drug suppression of the disease. Such attempts were made as in September 1942 in one area of high malaria incidence, when a command directive ordered that Atabrine (quinacrine hydrochloride) in doses of 0.2 gm. twice weekly be taken prophylactically but because of accumulation should be replaced after 3 months by quinine for 1 month. With these early efforts at suppressive drug control, malaria rates of combat troops in the range of 1,500 to 2,000 per 1,000 troops per annum were common.[2]

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[1] Boyd, M. F.: An Historical Sketch of the Prevalence of Malaria in North America. Am. J. Trop. Med. 21: 223-244, March 1941.

[2] Downs, W. G., Harper, P. A., and Lisansky, E. T.: Malaria and Other Insect-Borne Diseases in the South Pacific Campaign, 1942-1945. II. Epidemiology of Insect-Borne Diseases in Army Troops. Am. J. Trop. Med. (supp.) 27: 69-89, May 1947.

FACTORS IN EARLY FAILURES IN SUPPRESSION OF MALARIA

Experiences such as these soon led to the conclusion by line officers and most medical officers as well, that Atabrine was ineffective in suppressing clinical malaria under the conditions of combat. Quinine was in short supply, but it was widely believed that quinine would provide effective suppression and that Atabrine was a necessary but poor substitute for it. Furthermore, when Atabrine was initially administered it frequently led to nausea, vomiting, and diarrhea. This was particularly likely to occur when the administration was begun on shipboard, where anxiety and seasickness contributed to the prevalence of gastrointestinal upsets. Confusion, too, between the skin discoloration due to Atabrine and cases of infectious hepatitis (a confusion added to by some medical officers) increased fear of the drug. There were rumors that Atabrine caused impotence. In addition, soldiers soon learned that if they acquired malaria they would be removed from combat areas to more adequate hospital facilities. Altogether, the value and safety of administration of this drug was not wholeheartedly accepted by the troops, and forward medical officers themselves became lukewarm regarding it. Diminishing supplies of quinine were frequently given by the medical staff to their fellow officers. The result of all this was poor discipline in the use of suppressive therapy and consequent failure in control of clinical malaria.

The change in the attitude of command and medical officers alike toward Atabrine and its role in the malaria problem was aided by an important study [3] in an Army medical center located in Australia. This study was conducted by Lt. Col. (later Col.) Garfield G. Duncan, MC, Consultant in Medicine, Sixth U.S. Army, shown in figure 59, explaining the details of malaria suppressive therapy to Gen. (later General of the Army) Douglas MacArthur, Supreme Commander, Southwest Pacific Area. Here, a group of men, all known to be subject to recurrent malaria attacks, were gathered in a region free of endemic malaria and given suppressive amounts of Atabrine. Various dosage schedules were employed, including 0.1 gm. daily for 6 days each week and 0.5 gm. on 2 days of each week. There was prompt cessation of clinical malaria, despite vigorous training which included a final forced march of 25 miles.

This study pointed out the advantage of the twice weekly suppressive dose. Rigid supervision to insure the actual ingestion of the prescribed amount was more easily accomplished twice weekly than daily. Further, this dose, in all probability larger than absolutely necessary for good suppression, provided an additional margin of safety.

When this suppressive regimen was tried in a malarious area during combat, the results were even more impressive. Malaria rates as high as 1,230 per 1,000 per annum had been observed in a battalion supposedly receiving

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[3] Duncan, G. G.: Quinacrine Hydrochloride as a Malaria-Suppressive Agent for Combat Troops. War Med. 8: 305–318, November-December 1945.

0.6 gm. of Atabrine weekly but obviously without adequate supervision. When the dosage was changed to 0.5 gm. twice weekly, the attack rate dropped to zero within 24 hours, and not a single attack occurred during the next 2 months.

This and a number of other careful studies clearly established the importance of making absolutely certain that the men actually swallowed and retained the prescribed dose of Atabrine. This so-called Atabrine discipline,



U.S. Army photograph

FIGURE 59. Lt. Col. Garfield G. Duncan, MC, explaining the malaria suppressive therapy charts to Gen. Douglas MacArthur at the 101st Station Hospital, Rockhampton, Queensland, Australia, 26 November 1943. Left to right: Colonel Duncan; two officers in doorway unidentified; Lt. Col. Wallace A. Dunton, Sixth U.S. Army Training Center; Lt. Col. C. H. Morehouse, Aide-de-Camp to General MacArthur; Lt. Gen. Herbert Lumsden, British Army Liaison Officer; Lt. Gen. Robert L. Eichelberger, Commanding General, I Corps; Col. Frank LaRue, Commanding Officer, Sixth U.S. Army Training Center; and General MacArthur.

in default, certainly accounted for many of the failures of the drug as a suppressant early in the war.

There was, however, another factor that almost surely accounted for some failures even when the drug was faithfully ingested. Early in the war, the recommended dosage was small and had to accumulate to reach effective blood levels, as will be shown in more detail later (p. 473). This fact was not then recognized. Consequently, when troops began therapy shortly before or on the day of exposure, clinical malaria could appear before the concentration of Atabrine in the blood was sufficient for suppression.

The experience of 840 men in a construction group which landed on Guadalcanal in December 1942 illustrates this point well.[4] The men had never been exposed to malaria before, and on the day of landing, Atabrine in dosage of 0.4 gm. per week was begun. It was alleged that the drug was taken faithfully. In the third, fourth, and fifth weeks, 119 cases of clinical malaria developed, a rate of 1,523 per 1,000 per annum. Beginning with the sixth week, and coinciding with the predicted time of maximum blood concentration, the cases began to level off to about seven per week. As will be shown later, 0.4 gm. of Atabrine per week never produces a blood level adequate to suppress all malaria and has very limited effect until the maximum concentration is obtained from the seventh week on.

EFFECTS OF ATABRINE WITHDRAWAL

In most theaters of operations, there were either nonmalarious or relatively well sanitated base sections. When combat conditions permitted, troops were usually moved to such rear areas for rest and rehabilitation. It was thought that after long suppressive therapy, especially with, in addition, the debilitating influences of forward area duty, Atabrine would no longer effectively suppress clinical malaria. Administration of Atabrine was usually terminated in such troops unless local conditions made further disease transmission likely. Withdrawal of Atabrine was made either abruptly or after preliminary attack therapy with various combinations of Atabrine, quinine, or plasmoquin.[5] It was hoped that troops so treated would be freed, at least in part, of malaria and be less likely to suffer supposed damage from the cumulative effects of long continued Atabrine therapy. Finally, it was thought that, after a period without Atabrine, they might be more susceptible to its suppressive effect when they had to return to highly infective areas.

The results of this experiment were appalling. Depending upon the degree of seeding, malaria rates in such troops rose to peaks as high as 15,000 per 1,000 per annum, and sustained rates over a period of months of 3,000 to 4,000 per 1,000 annum were common.[6] With some of the strains involved, attacks followed attacks rapidly. It was common to have men hospitalized for the treatment of clinical malaria stricken with a fresh attack before completing the accepted period of convalescence. In one group studied in the South Pacific Area, the interval between attacks of malaria due to *Plasmodium vivax* averaged 28 days. The type of therapy that had been given had no significant influence upon the number of relapses or the interval between them in heavily seeded troops.

Such men, removed from suppressive therapy, were no longer fit for combat duty. The general physical fitness of the troops deteriorated; morale

[4] Personal communication, Paul Harper to author.

[5] Downs, W. G.: Results in an Infantry Regiment of Several Plans of Treatment for Vivax Malaria. Am. J. Trop. Med. 26: 67–86, January 1946.

[6] See footnote 2, p. 465.

suffered; adequate training was impossible; and hospital facilities and the few convalescent and rehabilitation camps available were overtaxed. Many men as a consequence were evacuated to the United States, and others had to be reassigned to limited duty.

Gradually, it was realized that suppressive therapy should be continued during rehabilitation periods and that the only way of controlling the disease in troops from whom suppressive medication had been withdrawn was to reinstitute such therapy. These decisions were reached after careful studies [7] of the results to be expected. It was found that general physical and psychological fitness improved remarkably once current attacks of clinical malaria were prevented by suppression. It was furthermore found that fatigue, or exposure to cold, wet, and arduous combat conditions did not cause suppressed malaria to "breakthrough" provided discipline in the administration of Atabrine was good.

EFFECT OF SUPPRESSIVE THERAPY ON PARASITE SPECIES

In intensely malarious areas of the Pacific, the clinical disease that broke through poorly taken or otherwise inadequate suppressive medication was predominantly due to *Plasmodium falciparum*. On Guadalcanal, for example, in January 1943 the parasite species recovered during malaria attacks were distributed, as follows: [8]

	Percent
Plasmodium falciparum	55
Plasmodium vivax	24
Unidentified	19

When troops were removed to nonmalarious areas and suppressive therapy withdrawn, there was a progressive shift with time in this species distribution. For example, the same troops found to be infected on Guadalcanal with the parasites previously listed were found 5 months later to have clinical malaria from which micro-organisms were recovered, as follows:

	Percent
Plasmodium falciparum	0
Plasmodium vivax	99
Unidentified	1

Such observations from all parts of the world confirmed the view that all late relapsing malaria was caused by *P. vivax*, in accordance with the long-recognized tendency of this species to produce the most stubborn form of relapsing malaria. Gradually, it became apparent that Atabrine, even in suppressive doses, was curative for malaria due to *P. falciparum*.

A study by Col. Maurice C. Pincoffs, MC, which pointed out this, as well as other facts about Atabrine suppression, was carried out in New

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[7] See footnote 3, p. 466.

[8] Levine, N. D., and Harper, P.: Malaria and Other Insect-Borne Diseases in the South Pacific Campaign, 1942-1945. IV. Parasitological Observations on Malaria in Natives and Troops, and on Filariasis in Natives. Am. J. Trop. Med. (supp.) 27: 119–128, May 1947.

Guinea and Australia in 1943. A group of previously uninfected men were moved to a highly malarious area for a 44-day period. One group took no suppressive therapy and served as controls. Sulfamerazine was given in doses of 0.5 and 1.0 gm. daily to a second group. A third group was given 0.1 gm. Atabrine daily 6 days a week. In the control group of 51 men, 26 developed clinical malaria. In the group of 111 men on sulfamerazine, only two manifested this disease. None of the 107 men on Atabrine fell ill with malaria.

Following this 44-day period, all groups were removed to a nonmalarious area for a further 3 months' period of observation and all drugs withdrawn. Of the group treated with sulfamerazine, 36 percent developed clinical malaria due to *P. vivax* as opposed to 30.8 percent of the group treated with Atabrine, while not a single case of malaria caused by *P. falciparum* developed during this period of observation among the men who had received Atabrine. It is almost certain that malaria due to *P. falciparum* had been transmitted to them previously as 10 cases developed in the control group of 51 men.

Further evidence was provided by another study [9] carried out in Australia. Human volunteers were subjected to numerous bites of infected mosquitoes while on various suppressive regimens. The New Guinea strains employed were known to produce severe attacks of malaria due to *P. falciparum* and *P. vivax*, the latter with a high and rapid relapse tendency. Quinine sulfate proved to be greatly inferior to Atabrine as a suppressive drug. Several sulfonamides in doses of 1.0 gm. daily suppressed and cured most *P. falciparum* infections but were inferior to Atabrine in this respect. The sulfonamides proved very poor in their suppressive action on malaria due to *P. vivax*.

Atabrine was conclusively shown both to suppress and to cure all *P. falciparum* infections under the conditions of the experiment. This drug was also found highly effective in suppressing *P. vivax* infections, but when it was withdrawn clinical malaria caused by *P. vivax* regularly developed. Hard physical work, forced marches, extreme cold, anorexia, blood loss, and injections of insulin or Adrenalin (epinephrine) failed to alter the suppressive action of Atabrine.

There can be little doubt that the control of *P. falciparum* infections by even suppressive doses of Atabrine was in large measure responsible for the great rarity of cerebral malaria and blackwater fever in our forces. Because these manifestations of malaria are responsible for a large proportion of deaths from this disease, it is understandable why the death rate was so extraordinarily low. This in itself was a happy consequence of the enforced use of Atabrine due to inadequate supplies of quinine.

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[9] Fairley, N. H.: Chemotherapeutic Suppression and Prophylaxis in Malaria: An Experimental Investigation Undertaken by Medical Research Teams in Australia. Tr. Roy. Soc. Trop. Med. & Hyg. 38: 311-355, May 1945.

LONG-TERM CLINICAL EXPERIENCE WITH ATABRINE SUPPRESSION

Many examples are available of long-term observations in military units that served in highly malarious areas. They all illustrate in varying degree early suppressive failure, amazing rates of clinical malaria when suppressive medication was withdrawn, and finally good control of malaria when suppressive medication, under proper conditions of Atabrine discipline, was resumed.

One impressive example [10] of this frequently repeated experience was that of an infantry regiment in the South Pacific which landed on Guadalcanal in three echelons in December 1942 and early in 1943 when malaria transmission was at a high level. Atabrine in doses of 0.4 gm. per week was ordered. The malaria rates between December 1942 and May 1943 varied between a low of 405 and a high of 1,296 per 1,000 per annum. In May 1943, the regiment was removed to a nonmalarious island for rehabilitation and all suppressive medication was withdrawn. Various malaria treatment regimens were instituted in an effort to eliminate some of the malaria seeding present in the troops; nevertheless, for the next 7 months, the malaria rate varied between 1,836 and 3,132 per 1,000 per annum. The highest rate occurred in the third week in one segment of the regiment that previously had had the greatest exposure to malaria transmission, and in this group the incidence of clinical attacks exceeded 14,000 per 1,000 per annum. The highest regimental rate, however, occurred in the sixth month, indicating no tendency for these extraordinarily rapid relapses of malaria caused by *P. vivax* to diminish with time.

Rehabilitation of these troops had obviously not been accomplished. Their working efficiency was in fact, so severely depleted that they were returned to carefully supervised Atabrine suppression late in November 1943. At first, 0.4 gm. of Atabrine per week was given, but late in January 1944, the dose was increased to 0.6 gm. per week. As soon as this was done, there was a prompt and impressive control of the malaria rate with return of the working capacity of the organization.

Then, after 2 months' duty on a nonmalarious island, the regiment served for less than 3 months on an island where malaria transmission was very slight. Next, there was 12 months' service in a nonmalarious area, making a total of 18 months' service while on Atabrine suppressive medication with little or no additional exposure to malaria transmission. Atabrine medication was then terminated. Over the following 3 months' observation period, there was nothing like the increase in the attack rate that had followed initial deatabrinization exactly 2 years previously. Approximately 400 men had remained with this regiment from its early exposure to malaria on Guadalcanal in 1942 until the final termination of Atabrine suppressive medication in May 1945. The malaria experience of these men is shown in chart 25.

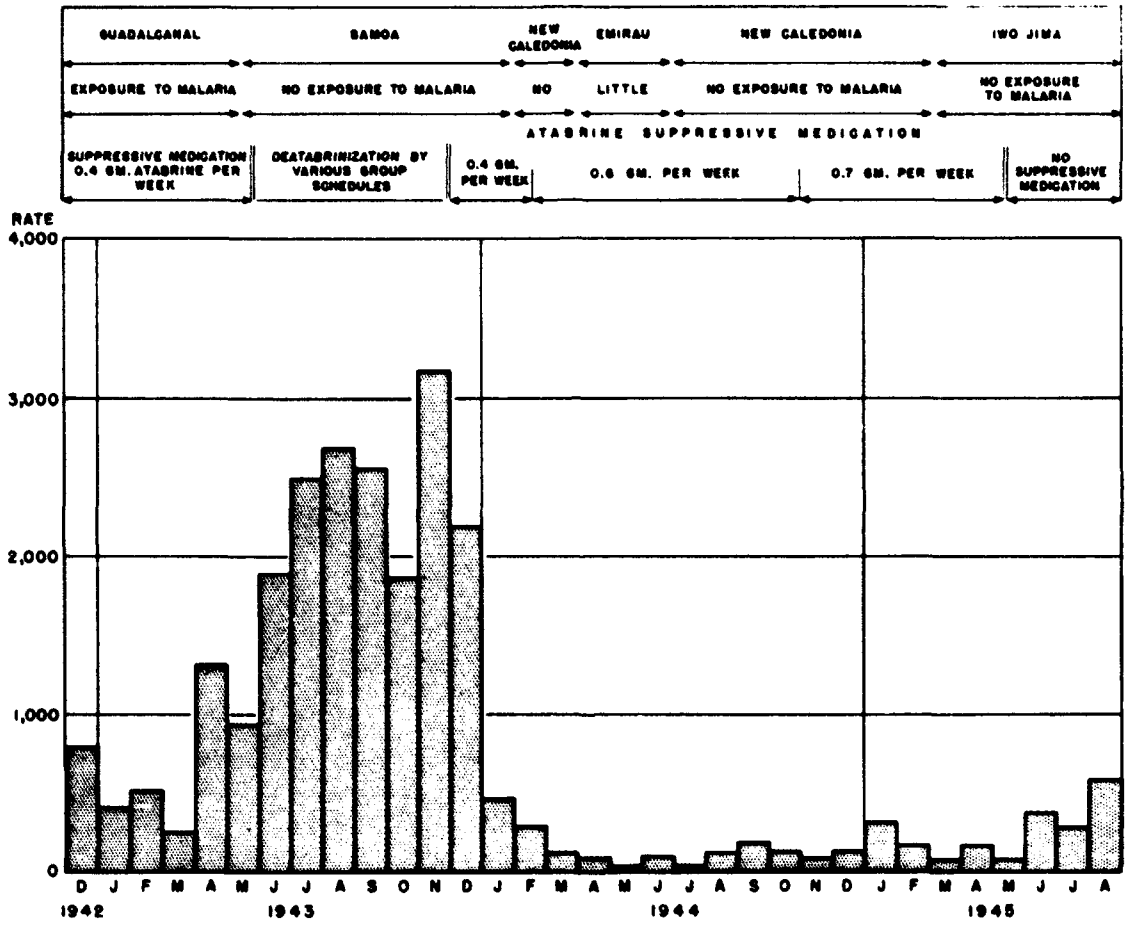
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[10] Baker, B. M., and Platt, D.: Vivax Relapse Rates Following Continued Atabrine Suppressive Medication: Observations on Malaria in an Infantry Regiment. Bull. Johns Hopkins Hosp. 81: 295–304, November 1947.

In review then, there was in this group a period of 6 months' extreme exposure to malaria, 7 months of attempted but unsuccessful eradication of malaria, and a final period of 18 months' excellent suppression of malaria by Atabrine with negligible fresh transmission. Suppressive medication was then terminated, but the latent malaria that developed during the next 3

CHART 25.—*Malaria experience of an infantry regiment carefully followed for 34 months, South Pacific Area, December 1942-August 1945*

[Rate expressed as number of cases per annum per 1,000 average strength]



Source: Modified from Baker, B. M., and Platt, D.: Vivax Relapse Rates Following Continued Atabrine Suppressive Medication: Observations on Malaria in an Infantry Regiment. Bull. Johns Hopkins Hosp. 81: 295-304, November 1947.

months was much lower in incidence than in the earlier period of Atabrine withdrawal. This was a unique experience in observing the effects of long-term suppressive therapy on troops heavily seeded with malaria, and there will probably never be an opportunity to confirm these observations. It seems likely, however, that the relatively low attack rate when suppressive therapy was finally terminated was due to permanent elimination of a significant amount of latent *P. vivax* infection either by the long-term drug therapy or by a gradual increase in biological resistance.

CONCENTRATION OF ATABRINE IN THE BLOOD AT LEVELS EFFECTIVE FOR SUPPRESSION

Basic understanding of optimum methods for suppression of malaria by Atabrine began only when field experience could be accurately controlled by determinations of the concentration of Atabrine in the blood. There were four large studies relating clinical effectiveness to Atabrine blood levels, and it is upon these that most of the accepted concepts of suppressive therapy depended. They were conducted in the United States,[11] in the Southwest Pacific,[12] and in the South Pacific.[13] Such field studies yielded a reasonably precise means of testing Atabrine discipline, made possible determination of effective suppressive dosage, and provided basic pharmacological information.

It was shown that when a constant dose of Atabrine is administered daily to a group, individual blood levels vary widely, but that individuals who attain high, average, or low blood levels, do so regularly. Furthermore, the group mean level can be calculated accurately and is a function of dosage and duration of administration. The maximum blood level yielded by a given dose is attained slowly over a period of 6 weeks, and then remains constant for the remainder of the period of drug administration. Fifty percent of the final equilibrium level is reached at the end of the first week, and 50 percent of each remainder in each of the 5 succeeding weeks. A dose of 0.4 gm. of Atabrine per week produces a group mean level at the end of 6 weeks of 12 μg. per liter; a dose of 0.6 gm. per week, a level of 18; and a dose of 0.7 gm. per week, a level of 21. A group mean level of 21 μg. per liter can be achieved either by giving a daily dose of 0.1 gm. for 6 weeks or by administering 0.3 gm. daily for 4 days. Once the desired level has been attained, regardless of whether this is done with small doses over a long period or by larger doses in a few days, the group mean level can be maintained by the daily administration of the dose that would yield that level after 6 weeks of daily administration.

Interest naturally was strong in determining the blood levels that would protect working troops from primary and from relapsing attacks of malaria. One study addressed to this question was made in a segment of a division heavily seeded with malaria. Without suppressive medication, the troops were having a malaria rate that varied between 2,000 and 4,000 per 1,000 per annum. Two groups of 600 men each were selected for the study. One group

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[11] (1) Final Report on Investigation of the Effects of Activity and Environment on Atabrine Therapy, Project No. 18, Armored Research Laboratory, Fort Knox, Ky., 23 Dec. 1943. (2) Shannon, J. A., Earle, D. P., Jr., Brodie, B. B., Taggart, J. V., and Berliner, R. W.: The Pharmacological Basis for the Rational Use of Atabrine in the Treatment of Malaria. J. Pharmacol. & Exper. Therap. 81: 307-330, August 1944.

[12] Bang, F. M., Hairston, N. G., Maier, J., and Trager, W.: Studies on Atabrine (Quinacrine) Suppression of Malaria. I. A Consideration of the Individual Failures of Suppression. Am. J. Trop. Med. 26: 649-661, September 1946.

[13] Schaffer, A. J., and Lewis, R. A.: Atabrine Studies in the Field. I. The Relation of Serum Atabrine Level to Breakthrough of Previously Contracted Vivax Malaria. Bull. Johns Hopkins Hosp. 78: 265-281, May 1946.

was given 0.1 gm. of Atabrine three times daily for 1 week (yielding a group mean Atabrine level in excess of 21 μg. per liter). Half of this experimental group then took 0.1 gm. Atabrine daily and the other half 0.05 gm. daily. The second group of 600 men had no medication and served as controls. During 4 weeks of observation, 157 of the controls but only 14 of the group on suppressive treatment developed clinical malaria. It was of interest that the Atabrine blood levels of these 14 treated men were all considerably lower than those of the treated group that remained free of clinical disease. In order to investigate the relationship of Atabrine blood levels to the probability of breakthrough of malaria, plans were made to expand the study with larger numbers of subjects.

A moderately seeded infantry division in a malaria-free area was selected. For longer than 10 months, these troops had had suppressive medication, first 0.4 gm. Atabrine per week and later 0.6 gm. per week, continuing on the latter dose when transferred to the rehabilitation area. Results of the study were as follows:

1. *Preliminary Atabrine serum levels.*—Of the nine infantry companies, 1,021 men had serum determinations made as soon as possible after reaching the rehabilitation area. Suppressive Atabrine was ordered, but as yet no special effort has been made to improve Atabrine discipline. Of this group, 65 percent had Atabrine levels of 19 μg. per liter or less. The arithmetic mean level of the entire group was 13 μg. per liter whereas the arithmetic means in the various companies varied between 9 and 20 μg. per liter. Obviously, some officers were enforcing more rigid Atabrine discipline than others. To confirm this conclusion, a large group of men were assured protection from disciplinary action and confidentially questioned regarding their actual intake of the ordered medication. Of those who claimed to have taken the suppressive doses faithfully, only 27 percent had acquired malaria, whereas 50 percent of those who admitted to poor discipline had the disease. Furthermore, relapses had been four times more frequent in those who admitted to disobeying orders as to Atabrine intake.

When this information was presented to command, extraordinary precautions were taken to see that all men who were offered six Atabrine tablets a week actually swallowed them. The arithmetic mean of the serum Atabrine levels of one company rose in 4 weeks from 11 to 20 μg. per liter with a sharp concomitant reduction in that company's malaria rate.

2. *Atabrine levels at time of breakthrough.*—Serum Atabrine levels were determined in 410 soldiers at times when they developed clinical malaria. Of these men, 97.4 percent had Atabrine levels of 10 μg. per liter or below with an arithmetic mean in this group of 5 μg. per liter. This figure should be compared both with the arithmetic mean of 13 μg. per liter of the "suppressed" group just discussed, and with the mean level of 20 μg. per liter achieved in the best disciplined company, which had no clinical malaria during the study period.

3. *Controls.*—In this same division, 404 men belonging to one company were removed from all suppressive medication at the beginning of the study. This control group had a malaria rate of 1,340 per 1,000 per annum as compared with the rate of 212 per 1,000 per annum in the group given suppressive treatment.

A roughly similar study [14] was conducted in an intensely malarious area at a time when an epidemic of malaria due to *P. falciparum* developed in an infantry regiment in combat. Again it was demonstrated that the Atabrine blood levels in "protected" troops were significantly higher than those in men who developed clinical malaria, this difference presumably being a result of better discipline in the former. There was suggestive evidence in this study that it took a higher blood level of Atabrine to suppress primary malaria caused by *P. falciparum* during combat than to suppress relapsing malaria due to *P. vivax* in a rear area. This impression, however, was not confirmed beyond question, although another study [15] in another area also suggested this conclusion.

This last was a further important study of the plasma levels of Atabrine in effective suppression, conducted in the Southwest Pacific. Again, it was demonstrated that there is no definite concentration in the plasma that divides protected individuals from those that break through suppressive therapy. However, it was pointed out that such plasma levels were obtained after the symptoms had started and might well have been quite different from those that prevailed at the time parasite multiplication began. Further, it was observed that the plasma level of Atabrine varied considerably during a 24-hour period depending upon the time the dose was given.

From this study, the conclusion was drawn that success of any suppressive program was related in part to the actual efficiency of Atabrine administration but that failure of suppression, even with low Atabrine plasma levels, was not always a result of failure to take the drug.

At the same time, it was realized, however, that during suppression there was no way to tell how much malaria was actually present though latent in troops. In the absence of this information, evaluation of any suppressive program could never be more than approximate. A study in the Southwest Pacific provided some information upon this important point.[16]

A previous study [17] had demonstrated that after the termination of attacks of clinical malaria by therapeutic doses of Atabrine a few parasites could

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[14] Final Report on an Investigation of the Blood Serum Level of Atabrine at Which Malaria Develops in a Hyperendemic Area. Special Report to The Surgeon General by Lt. Col. A. J. Schaffer, MC, and Capt. R. A. Lewis, MC, 3 July 1944.

[15] Bang, F. B., Hairston, N. G., Maier, J., and Trager, W.: Studies on Atabrine Suppression of Malaria. II. An Evaluation of Atabrine Suppression in the Field. Am. J. Trop. Med. 26: 753–759, November 1946.

[16] Bang, F. B., and Hairston, N. G.: Studies on Atabrine (Quinacrine) Suppression of Malaria. III. The Epidemiological Significance of Atabrine Suppression. Am. J. Trop. Med. 27: 31–38, January 1947.

[17] Bang, F. B., Hairston, N. G., Trager, W., and Maier, J.: Treatment of Acute Attacks of Vivax and Falciparum Malaria. Bull. U.S. Army M. Dept. 7: 75–89, January 1947.

often be found in the blood. These numbered usually less than one parasite per 500 leukocytes and always less than four per 500 leukocytes. Similar parasite studies were now conducted upon troops under suppression and not infrequently, even in the absence of symptoms and in the presence of adequate Atabrine plasma levels, there were positive blood smears. This was particularly true when the troops had previously had little clinical malaria. The more attacks they had had the less likely they were to have positive smears. When in such surveys the number of parasites found exceeded four per 500 leukocytes, careful inquiry and determination of plasma Atabrine levels usually disclosed that insufficient Atabrine had been ingested to prevent parasite multiplication.

When this method of study was applied to a group in which malaria was believed to be heavily seeded but well suppressed, parasites were found in the blood smears of 14 percent of the men. The degree of seeding of the group was subsequently shown by withdrawing suppression and observing that 80 percent of the entire group developed clinical malaria within an 8-week period.

Parasite surveys of this sort were correlated with malaria rates under suppression, Atabrine discipline and determination of Atabrine plasma levels. The conclusion drawn was that when the suppressive dose of Atabrine is 0.5 gm. twice weekly, protection is afforded roughly 98 percent of troops even though engaged in combat in a highly malarious area.

An important result of Atabrine suppressive therapy not generally appreciated goes more fundamentally beyond postponing the evil day of clinical attacks until suppression is withdrawn. Atabrine in suppressive doses faithfully taken not only kills the gametocytes of *P. vivax* but prevents the development of *P. vivax* and *P. falciparum* gametocytes.[18] Epidemics of malaria result from the availability of nonimmune susceptibles, anopheles mosquitoes, and gametocyte carriers. The latter can be controlled by Atabrine suppression and the relation of this control to outbreaks of malaria in troops was clearly demonstrated by observations in the Southwest Pacific.

UNDESIRABLE EFFECTS OF ATABRINE

Staining of the skin was a distinct detriment to the use of Atabrine as a suppressive agent. The sickly yellow hue of most soldiers who took the drug was unsightly, imposed an appearance of lack of vigor, and undoubtedly played a part in poor Atabrine discipline.

Gastrointestinal upsets resulting from Atabrine were not infrequent, particularly when the drug was first started and more particularly when loading doses were required. These initial intolerances almost invariably

[18] Bang, B. F., and Hairston, N. G.: Studies on Atabrine (Quinacrine) Suppression of Malaria. III. The Epidemiological Significance of Atabrine Suppression. Am. J. Trop. Med. 27: 31–38, January 1947.

subsided in time but they turned men from the drug in the beginning and some of them never accepted it willingly.

More serious reactions occurred in numbers that are not exactly known. It was demonstrated beyond question that Atabrine in doses employed in the treatment of clinical malaria caused some psychoses.[19] It seems probable that even in suppressive doses the drug made a contribution to less serious psychiatric disorders, but accurate information on this is not available.

A peculiar form of lichen planus was clearly related to Atabrine in suppressive doses.[20] A few cases of exfoliative dermatitis [21] were related causally but how much contribution suppressive Atabrine made to ordinary dermatological disorders cannot be determined.[22]

The subject of Atabrine toxicity is discussed more fully elsewhere in this history (p. 538). The attendant discomforts, and the small risk of more serious potential dangers, does not detract from the enormous contribution that suppressive therapy made to the maintenance of the effectiveness of troops throughout the war.

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[19] Newell, H. W., and Lidz, T.: The Toxicity of Atabrine to the Central Nervous System. Am. J. Psychiat. 102: 805–818, May 1946.

[20] Livingood, C. S., and Dieuaide, F. R.: Untoward Reactions Attributable to Atabrine. J.A.M.A. 129: 1091–1093, 15 Dec. 1945.

[21] Agress, C. M.: Atabrine as a Cause of Fatal Exfoliative Dermatitis and Hepatitis. J.A.M.A. 131: 14–21, 4 May 1946.

[22] Schamberg, I. L.: Studies on Post-Atabrine Dermatitis. II. Permanent Anhidrosis, Anhidrotic Asthenia and Prolonged Dermatitis Following Atabrine Dermatitis. J. Invest. Dermat. 21: 279–292, November 1953.

CHAPTER XVI

Clinical Aspects of Malaria

Harold D. Levine, M.D.

To most medical officers, malaria was a wholly new experience. By and large, they had never seen the disease before and were not likely to see it again. Except such textbook knowledge as they might possess, they had very little basis for comparison of its clinical features in World War II with previous observations. Perhaps for this reason, perhaps because interest in the bedside aspects of malaria was dwarfed by the tremendous advances made in the field of personal and group prophylaxis against the disease, amazingly few attempts were made to document its anamnestic features, symptomatology, and physical findings.

Another reason may underlie the dearth of clinical data on malaria during this war period. It is common experience that the clinical picture of a disease may be modified by its treatment, particularly if the treatment is effective. Thus, full-fledged use of digitalis, diuretics, and salt manipulations has modified the clinical characteristics of congestive heart failure. Likewise, the employment of antibiotics has altered the symptomatology of pneumococcal pneumonia. The same appears to have been true of malaria. In the overwhelming majority of cases, therapy was promptly effective in aborting the disease. Except during the very earliest phases of the war, when dosage was not yet adequate, and in some studies of recurrent cases, or in therapeutic malaria for neurosyphilis, in which treatment was deliberately withheld, the classical picture was blotted out in its earliest stages. Thus, the spontaneous pattern of a clinical attack of malaria was simply not observed in its entirety. To most physicians, therefore, malaria was a brief, grippelike illness with fever, chills and sweats, headaches, and generalized aches and pains.

Source material for the present review consists of a small collection of documents, official and nonofficial, particularly the reports from those theaters of operations where malaria rates were highest; namely, the Mediterranean (formerly North African) Theater of Operations, U.S. Army, and the South and Southwest Pacific Areas. A number of thoroughgoing studies of relapsing malaria due to *Plasmodium vivax* were also conducted in the Zone of Interior at Harmon General Hospital, Longview, Tex. The author has also drawn upon a number of publications in the medical literature and, of necessity, from his personal experience with the disease. A convenient baseline against which wartime clinical experiences with malaria may be compared is a series of papers entitled "The Infection in the Intermediate

Host," which appeared in "A Symposium on Human Malaria" published by the American Association for the Advancement of Science in 1941.

PREDISPOSING FACTORS

There appeared to be two factors in determining whether a clinical attack of malaria, either initial attack or relapse, would be precipitated. One was the intrinsic or host factor; after the earlier phases of the war, this boiled down simply to the question whether the soldier was receiving optimum suppressive doses of Atabrine (quinacrine hydrochloride). In the absence of adequate prophylaxis, a number of extrinsic factors, such as injuries, acute illnesses, and surgical operations, appeared to be capable of upsetting the delicate physiological balance between the micro-organism and the host. It was common to find malaria developing on surgical, orthopedic, or general medical wards. In the Mediterranean theater, Lt. Col. (later Col.) James B. McLester, MC, noted, during a period when malaria transmission probably did not occur, that malaria made its appearance in about 5 percent of patients with atypical pneumonia, in a similar percentage of patients with infectious hepatitis, and in about 1 percent of those with trenchfoot.[1] Other factors that were thought to be important in activating the disease were fatigue or exhaustion, hemorrhage, alcoholic bouts, the use of anesthetics, or exposure to extreme or sudden changes in temperature. There seemed little doubt that once the stage was set, any one or more of these factors could trigger a clinical attack. Contrariwise, it must be stated that in numerous trials it was demonstrated conclusively that even excessive physical activity was not a cause of breakdown of Atabrine suppression ("breakthrough").

In addition to these intrinsic (host) and extrinsic (environmental) factors in the precipitation of a malarial paroxysm, there was the parasite factor. It is well known that there are certain attributes resident in the individual *Plasmodium* itself that must not only determine whether a paroxysm will be inducted but what sort of clinical picture it will present. In short, although the malarial fevers possess certain common characteristics, they are actually a group of several distinct entities each with its peculiar attributes and individual potentialities.[2] Most descriptions of the disease available to the writer, however, failed to distinguish between the various plasmodial species responsible for the attack. In the text that follows, a description referring to a definite species can be assumed by the reader to be an exception to this generalization either stated in the quoted document or personally known to the author.

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[1] McLester, J. B.: Relapsing Malaria. M. Bull. Mediterranean Theat. Op. 3: 111–113, April 1945.

[2] Kitchen, S. F.: Symptomatology: General Considerations. *In* Malariology, A Comprehensive Survey of All Aspects of This Group of Diseases from a Global Standpoint. Philadelphia: W. B. Saunders Co., 1949, pp. 966–994.

PRODROMAL SYMPTOMS

Especially in cases that began insidiously, it was very difficult to draw a dividing line between prodromal symptoms and the actual onset of an attack of malaria. Patients with a brisk onset often stated that they had felt perfectly well on the preceding day. When prodromata were described, they lasted 2 or 3 days and were generally the usual symptoms of the frank attack presenting in lesser intensity. The most frequent complaints were headache, backache, weakness, and generalized aches. In a study at Harmon General Hospital of 435 soldiers with malaria due to *P. vivax* who were permitted to relapse, three-fourths had prodromal symptoms.[3] Most of these patients could reliably predict the imminence of an attack.

CLINICAL SYMPTOMS OF THE ACUTE ATTACK

Headache.—Headache, generally severe, of a pounding character, and frontal or bitemporal in distribution, occurred in almost all cases. In some, it was described as having a retrobulbar component. In general, this symptom outlasted the fever and other symptoms by several days. In *Plasmodium falciparum* cases, it was occasionally the harbinger of an impending cerebral syndrome.[4] In some cases there was an associated meningismus.

Chill.—In 80 percent of the attacks observed in the study at Harmon General Hospital, there was an acute rigor or chill; in another 8 percent, there was at least a sensation of chilliness.

Fever.—The great majority of patients showed fever peaks ranging from 102° to 105° F. by mouth. Since the response to treatment was generally prompt and convincing, the fever was generally interrupted after one or two peaks so that the remainder of the spontaneous febrile pattern of the attack was not observed. In the study made by Gordon and his coworkers, well over 80 percent of patients had thus attained a normal temperature after 3 days of treatment, and over 90 percent by 5 days after the beginning of treatment. Although the war experience afforded some opportunity to study the detailed morphology of the fever course in the various forms of malaria, a careful documentation of intermittency, remittency, periodicity, regimentation, anticipation, postponement of fever peaks, continued fever, or of the fever spikes characterized as being broad based or narrow based, could not be found. Nor is it clear that this would have served a useful purpose.[5] In the Southwest Pacific Area, remittent quotidian fever was seen more often

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[3] Gordon, H. H., Lippincott, S. W., Marble, A., Ball, A. L., Ellerbrook, L. D., and Glass, W. W., Jr.: Clinical Features of Relapsing Plasmodium Vivax Malaria in Soldiers Evacuated from the South Pacific Area. Arch. Int. Med. 75 : 159–167, March 1945.

[4] All material on malaria in the Mediterranean (formerly North African) Theater of Operations, U.S. Army, except when otherwise noted, is taken from Golz, Harold H.: Human Malaria in the North African and Mediterranean Theaters of Operations, U.S. Army. [Official record.]

[5] Kitchen, S. F.: Falciparum Malaria. *In* Malariology, A Comprehensive Survey of All Aspects of This Group of Diseases From a Global Standpoint. Philadelphia: W. B. Saunders Co., 1949, pp. 995–1016.

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than anticipated and this apparently without regard to species identification. In general, initial attacks were much more likely to be characterized by continued fever and relapses by a hectic fever.

Sweats.—Profuse perspiration was characteristic of the overt paroxysm. A few observers felt that a sweat out of proportion to the fever in the absence of an antecedent chill was actually a helpful aid in the diagnosis of malaria.

Splenomegaly.—At a Marine installation in Oregon,[6] splenomegaly was noted in less than 5 percent of cases acquired in the Southwest Pacific Area, even after 20 to 30 recrudescences. Transient splenomegaly, generally of only mild degree, was detected in only about 8 percent immediately after acute attacks of malaria caused by *P. vivax*. Such experiences are in conformity with previous observations regarding splenomegaly in malaria. Increase in the size of the spleen apparently depends upon the possession of some degree of immunity. It is also well known that the enlargement rapidly diminishes on cessation of the paroxysm, particularly if interrupted by treatment. In a tabulation of the symptoms of malaria as observed in the Mediterranean theater, based upon a questionnaire sent to medical officers, splenomegaly was reported in a range of from 27 to 85 percent. This wide divergence was attributed to differences in the thoroughness with which the examination was conducted. A low incidence was, however, reported from all other theaters and is probably real. What enlargement took place was not striking and was generally transient. This low percentage of palpable spleens stands in marked contrast to the accepted high incidence of this finding in seasoned immune natives exposed presumably to the same malarial parasites as were these unseasoned, nonimmune troops.

American medical officers who had the opportunity of working with Australian medical officers learned one technique of palpating spleens which is worthy of repetition. So far as this author knows, the method is virtually unknown in the United States. It consists in having the patient sit up in bed drooped forward over his knees. A remarkable degree of relaxation of the abdominal muscles is often thus attained. With the examiner at the patient's back, the fingers of both of the examiner's hands are curled around the left lower flank of the patient while the patient takes deep breaths. Frequently, the palpating fingers can extend well up under the rib margin. In a number of cases, the spleen can be felt by this method and by none other. The technique is perhaps best adapted to young individuals of military age.

Hepatomegaly.—In a considerable percentage of cases, the liver was palpable one or two fingerbreadths below the right costal margin, firm, sharp, and slightly tender. Kern and Norris found such involvement in 60 percent

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[6] Coggeshall, L. T.: Malaria and Filariasis in the Returning Serviceman. Ninth Charles Franklin Craig Lecture. Am. J. Trop. Med. 25: 177–184, May 1945.

of 1,153 cases of malaria seen on a hospital ship.[7] In the North African-Mediterranean theater this was noted in from 5 to 20 percent of cases. In the Southwest Pacific Area, this finding actually approached or exceeded the frequency of splenomegaly. This may be due to the fact that slight degrees of hepatomegaly are more readily detected than the slight degrees of splenomegaly that occur in nonimmune, promptly treated soldiers. It is conceivable, although less likely, that this discrepancy is related to a predilection of the Southwest Pacific malarial strains to liver involvement. This observation appears to have been anticipated by the peacetime findings of Gunther,[8] who noted the frequent finding of tenderness in the right hypochondrium in New Guinea malaria. He designated this as gallbladder tenderness.

Lymphadenopathy.—It was the observation of the author that the most common cause of slight to moderate degrees of generalized glandular enlargement in the Southwest Pacific Area was malaria. The pronounced grade of enlargement characteristic, for example, of scrub typhus was never observed in malaria.

Abdominal symptoms.—Half of the patients complained of abdominal pain. This was more frequent on the left than on the right side and occasionally radiated to the left lower chest. When bilateral it was generally sharper on the left. Although this was attributed to splenomegaly, the spleen was felt in only a minority of these patients. In a quarter of the patients the left side of the abdomen was tender; in some there was tenderness on the right side as well, generally in the right upper quadrant. Nausea occurred in 59 percent, and vomiting in 36 percent of attacks, but troublesome vomiting was very infrequent. The relative role of treatment with quinine or Atabrine on the one hand, and of the disease itself, on the other, in the development of these symptoms was uncertain, since treatment was started promptly in the great majority of cases. Diarrhea was not uncommon as the presenting complaint in uncomplicated malaria, regardless of type, in tropical areas where it occurred in mild form in about 10 percent of cases. This symptom was no more common in *P. falciparum* cases but when present was more severe and at times dysenteric and associated with bloody stools.[9]

Upper respiratory symptoms.—These were quite common and almost certainly a part of the disease itself. The most common symptom was a dry, painless cough. This was generally associated with musical rales, squeaks, and groans throughout the lung fields, signs quite characteristic of bronchial asthma but disappearing promptly on therapy. Coryza and bronchitis were less frequent manifestations. Malaria was frequently associated with bronchitis, and roentgenographic examination frequently showed infiltrations inter-

[7] Kern, R. A., and Norris, R. F.: Liver Involvement in Malaria. U.S. Nav. M. Bull. 43: 847–858, November 1944.

[8] Gunther, C. E. M.: Practical Malaria Control. Sydney: Consolidated Press, Ltd., 1943, p. 47.

[9] Hughes, S. B., and Bomford, R. R.: Clinical Features and Treatment of Malaria in British Troops in West Africa. Brit. M.J. 1: 69–73, 15 Jan. 1944.

preted as the result of complicating viral or bacterial pneumonia. It would be difficult to determine to what extent these were actually part and parcel of the malarial infection.

Miscellaneous symptoms.—Herpes labialis was seen in a rather high percentage of cases in the Mediterranean theater. Urticaria, generally transitory, was occasionally seen, particularly in the earlier phases of the war when quinine was used more frequently. Tinnitus was noted in about a quarter of the cases. In most patients with this complaint, it was difficult to determine the relative role of the disease or the treatment in its development. Cerebral symptoms such as drowsiness, fainting, disorientation, change in disposition, or meningismus were complaints in a few cases of malaria due to *P. falciparum*.[10] The prompt subsidence of these symptoms in malaria caused by *P. vivax* led to the impression that they were the result of the associated fever per se and not of cerebral malaria. In the alleged instances of cerebral malaria due to *P. vivax* infection,[11] the possibility of an undetected mixed infection including *P. falciparum* cannot be excluded.

In one exceptional experience, a number of patients with malaria presented symptoms suggesting hyperthyroidism.[12] These individuals showed prominent eyes, loss of weight, sudoresis, wet palms, tachycardia, and fine tremor of hands and tongue. The basal metabolic rate was normal in these cases.

COMPLICATIONS OF MALARIA

In the past, involvement of every organ or organ system has been described as complicating malarial fever, particularly when caused by *P. falciparum*. These have generally been ascribed to capillary infarction resulting from agglutination of the parasites along the capillary endothelium. Experience in World War II emphasized the extreme infrequency of such complications in adequately treated malaria and recalled the admonition of Stratman-Thomas that "the innumerable clinical manifestations, symptoms and sequelae which have been ascribed to malaria are unflattering demonstrations of the imagination and credulity of the human mind."[13] The following manifestations appear, however, to be fairly well documented.

1. *Cerebral malaria.*—Almost without exception, malaria deaths were due to cerebral involvement.[14] A clear-cut picture of just what constitutes cerebral malaria was often difficult to draw.[15] Empirically, the term may be

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[10] Talbot, D. R.: New Aspects of Malaria. J.A.M.A. 123: 192-194, 25 Sept. 1943.

[11] McGinn, S., and Carmody, J. T. B.: Cerebral Symptoms in Malaria. U.S. Nav. M. Bull. 43: 1157-1162, December 1944.

[12] Weeks, D. A.: Observations on Malaria. U.S. Nav. M. Bull. 43: 1171-1177, December 1944.

[13] Stratman-Thomas, Warren K.: The Infection in the Intermediate Host: Symptomatology, Vivax Malaria. *In* A Symposium on Human Malaria. Washington: American Association for the Advancement of Science, 1941, pp. 183-189.

[14] (1) Russell, Paul F., West, Luther S., and Manwell, Reginald D.: Practical Malariology. Philadelphia: W. B. Saunders Co., 1946, p. 293. (2) Medical Department, United States Army. Preventive Medicine in World War II. Volume VI. Communicable Diseases: Malaria. [In preparation.]

[15] See footnote 11, above.

applied to any case exhibiting any one or more of the following findings: Meningismus, convulsions, persistent delirium, or well-defined neurological signs. An index of the prevalence of cerebral malaria in World War II may be taken from the records of one U.S. Army general hospital in India where in 6 months of 1943 there were 40 cerebral cases among 1,764 U.S. soldiers and 100 cases among 4,295 Allied personnel.[16] In the Mediterranean theater, when the bulk of our troops were in Italy, medical officers of approximately 25 evacuation, station, and general hospitals reported 163 cases of cerebral malaria. Of these, 144 were recognized as caused by *P. falciparum*, and 19 were ascribed to *P. vivax*. There were 11 deaths due to *P. falciparum* infections, and of these 8 were cases of cerebral malaria. Preliminary tabulations of individual medical records indicate that there were 57 deaths due to malaria, all forms, originating in the Mediterranean theater during the years 1942–45. Of these, 27 were due to *P. falciparum* infections. Usually, the symptoms made their appearance a week or so after the onset of the clinical attack of malaria, following a day or two of precoma with persistent vomiting, increasing restlessness, mental confusion, and severe headache, but sometimes cerebral malaria developed abruptly without warning even after 1 or 2 days of treatment. Blurring of vision or diplopia were not uncommon. Acutely developing psychotic or psychoneurotic states were particularly alarming.

After the onset of the syndrome, the patient might show a profound stupor deepening into a coma; he might develop convulsive seizures[17] or exhibit nuchal rigidity, maniacal states, or various reflex disturbances. The temperature would rise progressively or abruptly to extremely high levels before death. In many respects, the illness resembled meningitis, encephalitis, or severe typhus fever. The spinal fluid was generally under increased pressure. Half of the spinal fluids examined showed an increased globulin content and many showed cell counts ranging between 20,000 and 30,000. The blood smear often failed to reveal malarial parasites until after repeated examination. When recovery occurred, it was generally completed, although a few patients showed residual cranial nerve palsies, hemiplegia, paresis, or psychosis.

2. *Other involvement of the nervous system.*—In the Mediterranean theater, patients were seen with peripheral neuritis involving the lower extremities. Three patients exhibited transient blanching of the optic nerve, one facial neuritis and homolateral brachial neuritis. In one hospital in the Southwest Pacific,[18] 16 patients were seen with a severe irritative neuritis with hyperalgesia, hyperhidrosis, and increase in muscle tone with actual con-

[16] Fitz-Hugh, T., Jr., Pepper, D. S., and Hopkins, H. U.: The Cerebral Form of Malaria. Bull. U.S. Army M. Dept. No. 83, pp. 39–48, December 1944.

[17] Simpson, W. M., and Sageblel, J. L.: Symposium on First Year of Activities at U.S. Naval Base Hospital——; Cerebral Malaria. A Report of 12 Cases Encountered at U.S. Naval Base Hospital——. U.S. Nav. M. Bull. 41: 1596–1602, November 1943.

[18] Harvey, A. M.: A Type of Neuritis Associated With Malarial Fever. Bull. Johns Hopkins Hosp. 75: 225–231, October 1944.

traction occurring in bilaterally symmetrical areas, usually the forearm and hand. Milder forms of neuritis, occurring in 18 of 100 consecutive cases of malarial fever, presented only subjective manifestations with transient attacks of numbness and tingling. With recurrent attacks of malarial fever, the nervous symptoms increased. The majority of these cases were due to a mixed infection. Distinction had to be drawn between these neuritides and those following that almost ubiquitous tropical disease, cutaneous diphtheria.

3. *Blackwater fever.*—This was rare. Twenty-five cases of acute hemolytic anemia and hemoglobinuria were reported as blackwater fever from the South Pacific Area. There were three deaths in this group, a much lower mortality than is usual for blackwater fever. Fifteen of the twenty-five cases occurred in Negro troops stationed on one island.[19]

4. *Cardiac malaria.*—Functional cardiac disorders, such as irritable heart with tachycardia, premature beats, and systolic murmurs, were, of course, not extremely rare in patients during malarial attacks or between relapses. But true organic cardiac changes, such as cause death from myocardial inflammation or capillary infarction, were extremely rare.[20] These generally occurred in individuals with malaria due to *P. falciparum.* The author saw two such patients who developed severe cerebral malaria in the combat area, both cases caused by *P. falciparum.* One had auriculoventricular and intraventricular block and the other a moderately enlarged, possibly dilated heart. The subsequent fate of these soldiers could not be followed. Two other patients with *P. falciparum* infection died at a nearby hospital. Both showed agglutination of the parasites along the capillary endothelium in the myocardium.[21] This experience led to the suspicion that microscopic coronary occlusions might be as important a factor in fatal *P. falciparum* cases as occlusion of cerebral vessels.

5. *Rupture of the spleen.*—This was a rare complication corresponding with the low incidence of splenomegaly.

6. *Ocular complications.*—A few cases of iridocyclitis coincided with attacks of malaria. In one patient, transient edema of the cornea occurred in each of two attacks of malaria due to *P. vivax* in the Mediterranean theater.

7. *Medical shock.*—If nothing else was done about the ancient terminology of clinical malaria, the record was set straight regarding the obsolete designation algid malaria. The fact that this is nothing more nor less than medical shock complicating malaria[22] should have been acknowledged long before World War II. This reorientation is of more than academic importance for it provides the clinician with a whole group of well-recognized

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[19] Harper, Paul A., Butler, Fred A., Lisansky, Ephraim T., and Speck, Carlos D.: Malaria and Epidemic Control in the South Pacific Area, 1942-44, pp. 195-207. [Official record.]

[20] Sprague, H. B.: The Effects of Malaria on the Heart. Am. Heart J. 31: 426-430, April 1946.

[21] Merkel, W. C.: Plasmodium Falciparum Malaria; The Coronary and Myocardial Lesions Observed at Autopsy in Two Cases of Acute Fulminating P. Falciparum Infection. Arch. Path. 41: 290-298, March 1946.

[22] Kean, B. H., and Taylor, C. E.: Medical Shock in the Pathogenesis of Algid Malaria. Am. J. Trop. Med. 26: 209-219, March 1946.

therapeutic aids for the treatment of this serious complication. The discovery of adrenal hemorrhages in Filipinos who died with this syndrome[23] suggests the feasibility of steroid replacement therapy, but whether this would be a universal finding is not known.

CHRONIC MALARIA

All observers agreed that in the absence of other factors, such as concomitant infection or malnutrition, the classical textbook picture of chronic malaria was wasting, anemia, and splenic enlargement. It was not observed in the U.S. Army, where troops were well fed and given adequate suppressive therapy. The extraordinarily low incidence of splenomegaly and anemia has already been discussed. Due significance must be accorded the role of hydration and of slight loss of weight as early adaptive processes attending acclimatization to the Tropics—the former might suggest anemia; the latter, wasting.[24] In contrast to the native with chronic malaria, exhibiting the characteristic triad of intermittent fever, anemia, and splenic enlargement, the U.S. Army patients who were incapacitated between relapses presented complaints generally falling into four categories: (1) Neurocirculatory asthenia, (2) symptoms referable to the musculoskeletal system, (3) vague symptoms referable to the central or autonomic divisions of the nervous system, and (4) combinations of two or more of these three groups.[25]

A careful study was made of a very large number of soldiers suffering from repeated *P. vivax* relapses and who complained of not feeling up to their usual health between attacks.[26] These men described the following symptoms: Weakness, fatigability, tension, excessive sweating, headaches, exertional dyspnea, anorexia, palpitation, blackouts, insomnia, nervousness, splenic pain, muscle pain, indigestion, and urinary frequency. These symptoms were always extremely difficult to evaluate. Although another group of observers who thoroughly studied this symptom complex in 50 servicemen conceded that malaria itself might be of prime importance in its production,[27] it was their further conviction, strongly concurred in by others, that the way in which the individual adjusted himself to his malaria and to concurrent situational factors was more significant in the development of symptoms, in their perpetuation, and intensification. It was the impression of most medical officers that these were exaggerated symptoms in men who were actually more interested in returning to their homeland than in rehabilitation for active

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23 Garcia, Eusebio Y.: Malaria in War and Peace. Manila: Grace Trading Co., 1945, p. 49.

24 Lee, D. H. K.: The Human Body and Hot Environments; Factors Influencing Man's Reactions to Heat Stress. [Unpublished manuscript.]

25 Levine, H. D.: Medical Experiences With American Troops in the Pacific, With Remarks on the Diagnostic Value of Sternal Puncture in Malaria and on the Innocuousness of Hookworm Infection. New England J. Med. 235: 933-938, 26 Dec. 1946.

26 See footnote 3, p. 481.

27 Tumulty, P. A., Nichols, E., Singewald, M. L., and Lidz, T.: An Investigation of the Effects of Recurrent Malaria; An Organic and Psychological Analysis of 50 Soldiers. Medicine 25: 17-75, February 1946.

duty. In the majority of cases, the symptoms obviously were strongly conditioned by such factors as exposure to combat and adverse living conditions or previous personality problems. None of the patients complaining of dyspnea on exertion presented evidence of heart disease as judged by physical examination, exercise tolerance tests, roentgenographic examinations or electrocardiograms. A red blood cell count below 4 million was extremely rare. Half of them had weight losses of from 10 to 30 pounds. But no measurable damage or dysfunction of the organ systems could be found. These observers condemned the practice of repeated or prolonged hospitalization for these individuals, contact with neuropsychiatric patients, or with patients about to be returned to the United States.

RELAPSES IN MALARIA

The tendency of malaria due to *P. vivax* to recrudescence was well documented before World War II, and subspecies variability in this respect has been recognized.[28] Relapsing malaria caused by *P. vivax* in World War II should not therefore have been a surprise,[29] nor should the particular character of one *P. vivax* strain as contrasted with another.[30]

Accurate statistics are not available, but there can be little doubt as to the remarkable relapsing tendencies of the *P. vivax* strains in the South and Southwest Pacific Areas. The author first became aware of the magnitude of this problem while on detached service with an Australian hospital. The medical officers there, only recently returned from service in the Mediterranean, were appalled by the stubborn relapsing tendency of the New Guinea strains of *P. vivax*, contrasting with the relative infrequency of relapse in the strains to which they had become accustomed in the Middle East. That this was the result of species specificity was subsequently confirmed in reports from Europe and the Mediterranean and in experience at Harmon General Hospital with malaria inocula of Pacific and Mediterranean origin. With the Pacific strains, relapses occurred in 70 percent of cases, and 75 percent of the relapses developed within 60 days of completion of Atabrine therapy. In the Mediterranean strains, there was a much lower incidence of relapses (30.6 percent) and a much longer delay (150 to 200 days) before relapse. There was other inferential evidence that malaria caused by *P. vivax* in the South Pacific Area differed from the same type of malaria seen elsewhere. Of the men in that area, 57 percent had in excess of 14 acute attacks, some as many as 40. The relapses appeared moreover to have a greater rhythmicity and regularity than those caused by other strains.[31] It should be borne in mind that all the

[28] Hackett, L. W.: Malaria in Europe, An Ecological Study. London: Oxford University Press, 1937.

[29] Russell, P. F.: Lessons in Malariology From World War II. Charles Franklin Craig Lecture, 1945. Am. J. Trop. Med. 26: 5-13, January 1946.

[30] Essential Technical Medical Data, European Theater of Operations, U.S. Army, for May 1944, inclosure 17 thereto.

[31] See footnote 6, p. 482.

experience here described was derived chiefly from *P. vivax* infections contracted by persons who had no immunity whatever to malaria.[32]

Malaria caused by *P. falciparum* exhibited relatively little tendency to relapse in the Mediterranean and Southwest Pacific, and when relapse subsequently occurred in these cases, it was only occasionally due to this same micro-organism. It appears more than likely that their original infection was actually a mixed one, *P. falciparum* being the dominant organism in the first attack, the subsequent relapses resulting from the emergence of the originally recessive *P. vivax* strain.[33] Thus, in advance areas in the Southwest Pacific, *P. falciparum* infections accounted for about 40 percent of all attacks,[34] while in the rear nonmalarious areas *P. falciparum* was found in only 8 percent of cases, *P. vivax* in 68 percent. Such usurpation of the dominant role in the relapse by *P. vivax* was well known long before the war.[35] Quartan malaria has long been regarded as relapsing malaria par excellence, but experience with quartan malaria in World War II was too limited to justify more than passing mention.

SUPPORTING EVIDENCE FROM THE LABORATORY

Parasite identification.—Most of the time during the war, the diagnosis of malaria was made with positive support from the laboratory. The techniques principally used have been discussed elsewhere. Variable success was reported in experiences with sternal puncture. In a number of studies,[36] occasional marrow smears were reported positive when the thick and thin blood smears were negative. Subsequent improvement in the accuracy of routine blood examinations for malarial plasmodia, however, dampened interest in sternal puncture.

Blood studies.—The white blood cell count was generally below normal, usually in the range between 4,000 and 6,000 in the Mediterranean theater study. This fact was frequently of diagnostic significance. In a small percentage of cases, a more marked leukopenia (less than 3,000) was recorded. Leukocytosis was seen under three conditions; namely, in the presence of a concomitant or complicating bacterial infection, in some severe uncomplicated cases, and in cerebral malaria. In the latter groups, it was apparently related to necrosis of tissues. Mild lymphocytosis was the rule. In a series reported from the Mediterranean theater, 45 to 65 percent of the lymphocytes resembled those observed in infectious mononucleosis.

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[32] Dieuaide, F. R.: Chronic Relapsing Vivax Malaria in the Army, 1942-44. [Official record.]

[33] (1) Malaria in the First Marine Division While Staged in Base Section No. 4, 1943. [Official record.] (2) Metcalf, R. J., and Ungar, J., Jr.,: Relapsing Malaria: Analysis of Cases from the Solomons. U.S. Nav. M. Bull. 43: 859–870, November 1944.

[34] Baker, M. P., Lyman, J. R., and Coons, A. H.: A Summary of Three Months' Experience With Malaria at the 105th General Hospital, U.S. Army, Southwest Pacific Area, December 1942-February 1943. [Official record.]

[35] See footnote 28, p. 488.

[36] (1) See footnote 25, p. 487. (2) Jacobson, B. M., and Russell, H. K.: Sternal Puncture in Diagnosis of Malaria. U.S. Nav. M. Bull. 45: 429–432, September 1945.

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The reported incidence of anemia was variable. Only one instance of mild normocytic, normochromic anemia was found in a group of 50 well-studied patients with malaria due to *P. vivax* at the 118th General Hospital in the South Pacific.[37] This was the general experience. In the Mediterranean theater, however, 29.5 percent of patients with malaria caused by *P. vivax* had red cell counts of 4 million or less. Anemia was somewhat more common in malaria due to *P. falciparum*, particularly during or shortly after the paroxysm. Counts of less than 3½ million were stated to have been common in *P. falciparum* infections.

In a small percentage of cases, the sedimentation rate was increased. In about half of these, this finding was accounted for by some complicating infection; in the remainder, it was unexplained and presumably related to the malaria per se. Erythrocyte fragility was probably normal.

Serological tests.—The serological tests for syphilis were frequently positive for longer or shorter periods after the acute paroxysms. The exact incidence of this finding cannot be stated. Dawber[38] found false-positive tests in 12.5 percent of 64 cases of malaria, generally becoming seronegative in 10 days after the last chill. One case remained positive for 18 days. At the 118th General Hospital, 15.6 percent of 900 cases of malaria ascribed to *P. vivax* were positive to Kahn tests. In the South Pacific Area, false positive reactions were found in 51 percent by the Mazzini test, 47.5 percent by Kahn, 33.6 percent by Kline, 20.4 percent by Kolmer, 10.4 percent by Eagle, and 5.8 percent by the Hinton technique.[39] Rosenberg[40] likewise found that the Hinton test yielded the smallest proportion of falsely positive reactions. He found that the strongest false reactions were obtained between 7 and 10 days after the chill and persisted for 4 to 6 weeks. He felt that persistence of positive serology by any test beyond 6 weeks, in the absence of continued evidence of malarial infection, should arouse the suspicion of syphilis.

The complement fixation test for malaria in general gave unsatisfactory results. In the Mediterranean theater, this was attributed to a faulty antigen. The consensus furthermore was that the adrenalin provocation test (Ascoli) was not helpful in diagnosis.

A number of studies were made of liver function in malaria patients. A study of 317 patients with chronic relapsing malaria due to *P. vivax* at Harmon General Hospital disclosed transient disturbances of function but gave

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[37] See footnote 27, p. 487.

[38] Dawber, T. R.: On the Importance of Malaria as a Cause of False Positive Serologic Reactions. Ann. Int. Med. *19: 651–655, October 1943.*

[39] Simpson, W. M., Leake, W. H., McMahon, A., Gudex, T. V., and Rueckert, R. R.: Symposium on First Year of Activities at U.S. Naval Base Hospital——; Experiences With Malaria at an Advance Base in the South Pacific. Report of 4,647 Admissions at ——. U.S. Nav. M. Bull. 41: 1588–1595, November 1943.

[40] Rosenberg, A. A.: Effect of Malaria on Serologic Tests for Syphilis. Bull. U.S. Army M. Dept. No. 84, pp. 74–80, January 1945.

little or no indication of permanent hepatic dysfunction.[41] The percentage of abnormal response to tests was somewhat higher in a study conducted in North Africa, but this was not limited to *P. vivax* cases. In this latter group, the liver was enlarged in 20 percent of cases.

DIFFERENTIAL DIAGNOSIS

The morbid conditions that had to be differentiated from malarial fever were legion. They varied, of course, with geographic location. Thus, sandfly fever (in the Mediterranean), dengue or scrub typhus fever (in the Pacific), and pneumonia (in Panama)[42] had to be given important consideration. The medical school teaching that it is wisest in a given case to explain a symptom complex on the basis of a single diagnosis rather than multiple diagnoses was not justifiable in malarious areas. Malaria being almost ubiquitous, the medical officer had to be prepared to find it as a complicated or a complicating disease. When the smear was positive, the decision had to be made whether the *Plasmodium* was there as an active hidden partner or whether this finding represented a mere parasitic relapse of little or no clinical importance. Almost all of the patients with salmonellal infection described by Baker and Bragdon,[43] for example, showed smears positive for malaria. A large majority of the patients with scrub typhus fever who came to the 105th General Hospital in the Southwest Pacific had positive smears.

A complete elaboration of the different conditions that would have to be considered in the differential diagnosis would be too formidable a task to be undertaken here. Such a list would certainly have to include tuberculosis, typhoid fever, amebic and bacillary dysentery, amebic hepatitis, preicteric infectious hepatitis, meningitis, Hodgkin's disease, subacute bacterial endocarditis, leishmaniasis, and schistosomiasis as well as the conditions that have just been enumerated; namely, dengue fever, sandfly fever, salmonellal infection, and scrub typhus. At times, the symptoms of a paroxysm would simulate an acute surgical emergency, such as biliary colic, ruptured peptic ulcer, ruptured spleen, or acute appendicitis. And here again, with an established surgical condition, a complicating malarial infection was not uncommon. At the 105th General Hospital, for example, about a fifth of the patients with malaria were battle casualties on the surgical service. Hyman analyzed the records of 100 patients admitted to a naval base hospital in the Pacific with a diagnosis that was subsequently changed to malaria.[44] These

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[41] Lippincott, S. W., Ellerbrook, L. D., Hesselbrock, W. B., Gordon, H. H., Gottlieb, L., and Marble, A.: Liver Function Tests in Chronic Relapsing Vivax Malaria. J. Clin. Investigation 24: 616–622, September 1945.

[42] Applebaum, I. L., and Shrager, J.: Pneumonitis Associated With Malaria. Arch. Int. Med. 74: 155–162, September 1944.

[43] Baker, M. P., and Bragdon, J. H.: Septicemia Due to Salmonella Enteritidis. New England J. Med. 237: 175–179, 7 Aug. 1947.

[44] Hyman, A. S.: Clinical Masquerades of Malaria; Observations in South Pacific Combat Areas. U.S. Nav. M. Bull. 45: 287–303, August 1945.

cases fell into groups classified according to the major predominating symptom that led to the erroneous diagnoses, as follows:

Diagnoses		*Number*
Simulated diseases of the chest		34
With cardiac symptoms	21	
With pulmonary symptoms	13	
Diseases of the abdomen		26
Stomach	9	
Liver and gallbladder	8	
Spleen	6	
Appendix	3	
Diseases of the bones and joints		21
Diseases of the head		12
Brain	7	
Eyes	3	
Other	2	
Miscellaneous		7
Kidney	4	
Other	3	
Total		100

These diagnoses were made during the early days of the Solomon Islands campaign before most of the medical officers had become familiar with the bizarre manifestations of malaria and before an adequate schedule of Atabrine suppression had been worked out.

SUMMARY

When malaria was promptly recognized and effectively treated in the nonimmune American soldier it was generally a brief, grippelike illness with headache, backache, pain in the abdomen, chills or chilliness, nondescript fever, and sweating. These patients showed very little splenomegaly, more impressive hepatomegaly. Diarrhea and wheezing occurred in many of the acute cases. There was very little, if any, tendency to complication. Anemia was not a problem in *P. vivax* infection; in some *P. falciparum* cases it was a moderate and transient phenomenon. The Pacific strains of *P. vivax* showed an extraordinarily stubborn tendency to relapse. Disability between relapses was largely related to prolonged tropical or combat service, to ennui or nostalgia, or to the soldier's reaction to his illness. The mortality rate was phenomenally low. (See p. 460.) Death was generally the result of cerebral malaria due in most, if not all, cases to *P. falciparum*.

CHAPTER XVII

Treatment of Malaria

Perrin H. Long, M.D.

INTRODUCTION

An interesting commentary on the state of health of the people of the United States at the beginning of World War II was that the majority of physicians entering the Armed Forces had had practically no experience in the diagnosis or treatment of malaria. To be sure, in the medical school courses of clinical microscopy, each had studied stained slides showing malarial parasites, or if there happened to be a patient in the ward who had malaria inoculata, thick fresh films of blood might have been examined. Occasionally in seaports, sailors suffering from malaria were seen on the medical services, treated with quinine, and then discharged shortly after their fever had subsided. As far as malaria inoculata was concerned, the problem was often to keep the infection from dying out rather than to arrest it by treatment. The average younger American physician, except in certain rural areas in the Southern United States, hardly gave a thought to malaria and was *unconcerned* about his lack of knowledge of this disease.

When it became evident in May 1940 that the Armed Forces of the United States were going to be sharply augmented, the Surgeons General of the Army and the Navy requested Dr. Lewis H. Weed, then Chairman of the Division of Medical Sciences of the National Research Council, to set up certain consultative and advisory committees. One of the earliest of the groups formed by Dr. Weed was that which, under the chairmanship of Dr. Henry E. Meleney, devoted itself to problems of tropical diseases. Of course, malaria immediately became a prime subject for discussion by this group. Out of the work of this subcommittee came the initial recommendation for the suppression and treatment of malaria with quinine. Obviously in 1940 and during the first half of 1941, there was no positive indication that the Axis Powers would seize Indonesia, the main source of the world's supply of quinine. Although Atabrine (quinacrine hydrochloride) and certain other suppressive and therapeutic agents were carefully considered, their use for suppressive or therapeutic purposes at that time was always thought of as secondary to the use of quinine.

The military events that occurred late in 1941 and early in 1942 brought a rude awakening to all concerned with malaria in this country. With relatively small supplies of quinine on hand, the Japanese move into Indonesia and Malaya, which cut off the major source of quinine, brought the Subcommittee on Tropical Diseases, National Research Council, to the recom-

mendation that the military forces of the United States must rely on Atabrine for the suppressive and the specific therapy of malaria. At that time, there was relatively little in the U.S. medical literature concerning the properties of Atabrine, and very few American physicians had used it or, for that matter, even heard of it. Very little was known about its pharmacological or toxic properties. Schemes of therapy, either suppressive or definitive, were based on empirical observations or even guesswork. This was the status of affairs when the Office of Scientific Research and Development initiated its large-scale research project on Atabrine in 1942. One of the earliest applied projects was testing the drug in normal human beings over a period of weeks to determine its possible toxic effects when it was used for suppressive therapy over a long period. The dosage schedule employed was 0.1 gm. twice a week. Various social groups, such as students, reform-school inmates, and prisoners in penal institutions, were employed as test subjects in these early trials. One of the results of these trials was extraordinarily significant. But how significant it was, unfortunately, was not recognized until, at least in the North African (later Mediterranean) Theater of Operations, U.S. Army, serious, if not permanent, damage had been done to the minds of the military relative to the use of Atabrine for the suppression of malaria. It was noted that in the test subjects there were sharp, prostrating gastrointestinal attacks characterized by nausea, vomiting, and diarrhea following the third dose of the suppressive medication. This occurred very frequently in the student group, very much less frequently in the reformatory inmates, and least of all in the inmates of the State prisons. It was also observed that, if the therapy was continued, there were very few individuals who had to discontinue the Atabrine because of gastrointestinal disturbances following subsequent doses of Atabrine. It was further noted that, if the drug was given in dosages of 0.1 gm. per day, gastrointestinal disturbances were minimal.

In the North African and Mediterranean theaters, where everything having to do with malaria was a joint command and professional project between the British and Americans, and for a considerable period with the French and Italian forces, the author was a member of the Malaria Committee of Allied Force Headquarters. In January 1943, this committee began its discussion which led to a joint command directive regarding the use of Atabrine for the suppression of malaria. The author, remembering the gastrointestinal disturbances that occurred after the third dose in the trials in the United States, held out for a daily suppressive dose of Atabrine. The British and French members of the committee resolutely opposed this method of suppression. To make a long story short, the author was outvoted and, under the operational rules of Allied Force Headquarters, had to accept the committee's decision. On 22 April 1943, suppressive therapy was begun on a biweekly (Monday and Thursday) basis, 0.1 gm. of Atabrine per dose. No troubles were encountered after the administration of the first two doses. The third dose was administered to all troops at the evening meal on Thurs-

day, 29 April 1943. Within 4 or 5 hours, sharply defined toxic reactions characterized by varying degrees of nausea, vomiting, and diarrhea made their appearance. Curiously enough, military personnel stationed to the rear of combat elements suffered far more than the fighting men. Infantry units of the II Corps in combat in Tunisia had about 5 percent toxic reactions; whereas, in certain hospitals and headquarters units in the rear, more than 75 percent of the personnel were affected. As one of our British colleagues remarked the next day, "it had been a shaking experience."

Understandably, as reports of toxic reactions piled into Allied Force Headquarters from all over the North African theater, consternation prevailed, and there was an immediate demand that suppressive therapy be discontinued. Calm was eventually restored, faith in the use of Atabrine was reaffirmed officially, and suppressive therapy was continued. However, as can well be imagined, the damage was done, and it can be said that throughout the rest of the war, discipline relative to suppressive therapy was poor in many units throughout the theater. Then, to compound confusion, the first great seasonal epidemic of infectious hepatitis occurred in American troops beginning in August 1943, and in many quarters this epidemic was at first thought related to the use of Atabrine for the suppression of malaria. The author cannot determine, from the reports available to him, whether similar incidents occurred during the initiation of suppressive therapy with Atabrine in other theaters of operations. However, it appears that, in all areas in which there was fighting and malaria was epidemic, the discipline required to carry out successful campaigns for the suppression of malaria by the use of Atabrine was difficult to enforce and the terrific toll of ineffective military personnel resulting from malarial attacks was directly related to this lack of discipline. Command was not convinced of the value of suppressive therapy with Atabrine and did not, except in a few areas, take the steps necessary to make the suppressive program effective.

EXPERIENCE IN THE PACIFIC

Our military forces first felt the impact of malaria on their ability to wage war effectively in the South Pacific Area. The experiences with malaria in that area were so rich and varied, and such careful, large-scale studies were carried out on its nature and the suppressive and therapeutic problems it posed, the reader is referred to other volumes in the history of the Medical Department in World War II for statistical and other details.[1] The substance of these observations is in part summarized here, for their bearing on treatment.

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[1] (1) Medical Department, United States Army. Internal Medicine in World War II. Volume I. Medical Consultants. Washington: U.S. Government Printing Office, 1961, pp. 603-618. (2) Medical Department, United States Army. Preventive Medicine in World War II. Volume VI. Communicable Diseases: Malaria. [In press.]

In this as in other theaters, most medical officers early in the war had little practical knowledge of malaria. Some few had had clinical experience, mostly in the southeastern part of the United States, and they were disposed to ascribe "properties to quinine that it did not possess." Such "malaria experts" scattered through many medical units "were believed to have done much harm, for most of them preached quinine with evangelical zeal and blamed" everything, particularly the very difficult problem of controlling relapsing malaria, "on the enforced use of Atabrine." Quinine, in short supply, was limited by command to cases intolerant to Atabrine, and the problem of controlling relapse was not solved until experience had taught the proper use of Atabrine.

According to Col. Benjamin M. Baker, MC, Senior Consultant in Medicine, Office of the Surgeon, South Pacific Area, there were few cases of cerebral malaria (46), fewer still of severe anemia (14), blackwater fever (13), and splenic rupture (6). However, based on sample tabulations of individual medical records, there were no admissions for blackwater fever in the Central and South Pacific Areas during 1942–45. As in the Army as a whole, there were few deaths; in this theater, only 24 were attributed directly to malaria between 3 October 1942 and 1 September 1944. The more virulent infections caused by *Plasmodium falciparum* predominated during epidemics. Infections with the less virulent but stubbornly relapsing *Plasmodium vivax* appeared in increasingly higher percentages of cases when troops were removed from malarious to nonmalarious islands and suppressive Atabrine therapy gradually withdrawn. It was apparent that Atabrine, even in suppressive dosage, cured malaria due to *P. falciparum.* To this specific action of the drug has been ascribed the low death rate and the comparatively low incidence of malignant malaria in the Pacific areas. The most pressing concern of the U.S. Army was the very high relapse rate of *vivax* infections, immobilizing whole regiments of men.

The 147th Infantry Regiment met the enemy, both human and plasmodial, in Guadalcanal (1942–43), armed against the latter with suppressive doses of quinine for a short period, and Atabrine later. In May 1943, the entire regiment was sent to Samoa, a nonmalarious island. Here, Atabrine therapy was gradually withdrawn, and the men were given no further specific treatment until they developed fresh attacks, with the hope that their malaria would "burn itself out." The actual result was the development of chronic malaria with repeated relapses in the overwhelming majority. It was apparent that the suppressive therapy on Guadalcanal had cured few, if any, cases of malaria due to *P. vivax.* Massive therapy was also ineffective in curing latent *vivax* infections. Before the regiment could be returned to active duty, suppressive medication with Atabrine had to be reinstituted. This therapy effectively reduced the malaria rate, and the physical fitness of the regiment was restored.

Similar results followed a similar attempt to "demalarialize" the Americal Division on the Fiji Islands. Troops heavily seeded with malaria were not well enough to return to combat after many months of "demalarialization." Many patients were evacuated to the Zone of Interior, but many remained in the theater, relapsing repeatedly. The only reasonable course was to resume suppressive therapy with the hope, but as yet no certainty, that continued use would materially reduce the staggering noneffective rate.

An experiment was set up on the Fiji Islands with combat units engaged in maneuvers under conditions simulating those of jungle warfare. One group was given no suppressive therapy; the other, sufficient Atabrine to establish the blood levels that had been found to be effective. In the control group, the relapses continued to occur at about the same rate as during previous months; in the treated group, malaria was practically eliminated. The cases that did develop were in men who, like some others observed previously, exhibited consistently low Atabrine blood levels.

Subsequent to this study, troops were kept on suppressive medication whether they remained in malarious areas or were sent to nonmalarious regions for rest and recreation. First to come under the new policy was the 25th Infantry Division, which had become heavily seeded with malaria on Guadalcanal and was now removed to malaria-free New Zealand, where suppressive therapy was continued. After Atabrine discipline was tightened, the results were excellent.

Having proved feasible, the control of malaria by continued suppressive medication was required by military necessity. Experience had shown that Atabrine in suitable dosage (0.1 gm. a day) was an effective suppressive for most if not all primary malaria and, if continued, for recurrent attacks. Nevertheless, many questions remained in medical minds. Some feared that relapse was only being postponed to the day when Atabrine would finally be withdrawn. Some thought the parasite would acquire tolerance to the drug. Such considerations had an important bearing on plans for reemployment of highly malarialized troops, and on treatment of troops in malarious areas.

To provide answers to many questions, a large number of men of the 147th Infantry were followed from Guadalcanal (November 1942) to Iwo Jima (August 1945). Their medical history "included heavy exposure, light exposure, atabrinization, de-atabrinization, long-continued suppressive medication, and terminal de-atabrinization." The observations, made on the same experimental group and covering this not inconsiderable expanse of time, space, and experience, appeared to justify the conclusion that long-continued suppressive Atabrine therapy does, in fact, ultimately destroy a large amount of infection due to *P. vivax*. After 17 months of continuous suppression, all antimalarial therapy was discontinued, in the nonmalarious environment of Iwo Jima, 20 months after the last significant exposure to infection. During the ensuing 3 months, there was only a slight increase in the malaria rate in contrast to the violent outbreaks that had followed the initial deatabrini-

zation. It was, unfortunately, not possible to continue followup observations beyond this 3-month period.

In another comprehensive study, no serious aftereffects of malaria were found in soldiers who had been through many clinical attacks. Toxic reactions to Atabrine were not troublesome in the South Pacific Area. Signs of intolerance in the central nervous system appeared in a small group of cases and were carefully studied; they subsided when dosage was decreased. In comparative studies, other drugs (Plasmochin naphthoate (pamaquine naphthoate), the sulfonamides, totaquine) appeared to be generally inferior or not superior to Atabrine.

In the Southwest Pacific Area, important studies were carried out on suppressive treatment, such as those in Australia by Lt. Col. (later Col.) Garfield G. Duncan, MC, of the American Army and by Brigadier N. Hamilton Fairley of the British, and those by Lt. Col. (later Col.) Maurice C. Pincoffs, MC, and others in New Guinea. The observations made early in the war on that island were probably the first to demonstrate clinically that malaria caused by *P. falciparum* could be cured by Atabrine in suppressive dosage.[2] Subsequent studies by Bang and others showed that a certain concentration of the drug in the blood was necessary for protection against clinical attacks and that equilibrium could be achieved by giving 0.1 gm. daily for 6 weeks, or 0.3 gm. daily for 4 days, and could be maintained by continuing suppressive doses. It was shown that this treatment resulted in control of gametocyte carriers and this, in turn, prevented epidemic outbreaks of malaria when troops were exposed again to infection.

EXPERIENCE IN THE INDIA-BURMA THEATER

Malaria as constituting a major medical problem in the India-Burma theater has been presented in another volume in the history of the Medical Department in World War II, from which the following summary has been largely drawn.[3] It is obvious that in many instances information will overlap. In India, U.S. troops were exposed to malaria, most of them for the first time, in a vast region where the incidence was something like 4,000 per 1,000 per annum in the population. An overnight journey by train was likely to result in clinical malaria in 80 percent or more of the troops making the trip. The highest percentage of patients with malignant tertian malaria was seen in this theater; cerebral malaria was the principal clinical problem. Medical officers came from the United States unprepared for the multiform manifestations of the disease and were often, particularly at first, uncertain in diagnosis. As to treatment, there was much individual experimentation. This may have been due, in part, to the proximity of the Indian Medical Service and its methods of therapy; in part, to delays in receiving

[2] Baker, B. M., and Platt, D.: The Effect of Long-Continued Suppressive Atabrine Medication on Relapses of Vivax Malaria. Tr. Am. Clin. & Climatol. A. 58: 145–152, 1946.

[3] See footnote 1, p. 495.

information from the Surgeon General's Office on newer methods of treatment; and in part, perhaps, to the presence in Army hospitals of highly individualistic, research-minded medical officers.

The overall percentage of cases of malaria classified as cerebral, in the three hospitals where most of them were seen, was 1.9 percent. At the 20th General Hospital, the incidence was 2.3 percent for all patients with malaria and was 2.2 percent for Americans alone. At the 73d Evacuation Hospital, during a 6-month period, there were 57 cases of cerebral malaria with 27 fatalities, only 1 an American. At the 48th Evacuation Hospital, treating chiefly Chinese soldiers, between April 1944 and March 1945, the mortality was 43 percent, with no deaths in Americans. From September 1943 to May 1945, the 14th Evacuation Hospital had 121 cases with 33 deaths, all the fatalities occurring in Chinese patients.

P. falciparum was recognized as the causative agent in most cerebral cases; some few were ascribed to *P. vivax*. In the majority of all American patients with malaria, *P. vivax* predominated; in the majority of Chinese, *P. falciparum* predominated. Col. Francis C. Wood, MC, of the 20th General Hospital thought that an observation made there threw light upon this. Some Chinese patients were given no treatment for several days preparatory to testing with a new drug, at the request of Chinese medical officers. This was Fraxine, a preparation of unknown composition and, in the event, of no proved value. Of these patients, those with infections due to *P. vivax* became symptom free in 4 days without treatment; the infections with *P. falciparum* did not subside during this period. It appeared probable that Chinese soldiers infected with *P. vivax* recovered spontaneously and were usually not seen at hospitals.

The India-Burma theater was established in October 1944 when U.S. Army Forces, China-Burma-India, was divided into two separate theaters—the China Theater and the India-Burma Theater. What seems to have been the first publication in the theater on the treatment of malaria appeared in the opening issue of the *Field Medical Bulletin*, Headquarters, Services of Supply, U.S. Army Forces in China-Burma-India (August 1942). This was a summary of a pamphlet issued by the British War Office recommending treatment different from that advised in Circular Letter No. 56, Office of the Surgeon General, U.S. Army, 9 June 1941, entitled "A Note on the Treatment and Control of Certain Tropical Diseases." In the November 1942 issue of the *Field Medical Bulletin*, Maj. Sydney P. Waud, MC, and Maj. Robert S. Crew, MC, of the 159th Station Hospital, presented "several changes in the treatment of malaria," derived from the School of Tropical Medicine, Calcutta, India. Finally, the *Bulletin* in its January 1943 issue reprinted Circular Letter No. 135, Office of the Surgeon General, U.S. Army, dated 21 October 1942 and entitled "The Treatment and Clinical Prophylaxis of Malaria," but in the issue of February 1943, Lt. Col. Gordon S. Seagrave,

MC, expressed doubt concerning the efficacy of Atabrine and presented his own views on therapy including liquor arsenicalis and neoarsphenamine.

The theater as a whole continued to use the plan of treatment outlined in Circular Letters Nos. 135 and 33, the latter dated 2 February 1943 and entitled "Treatment and Control of Certain Tropical Diseases." Circular Letter No. 33 was replaced by Circular Letter No. 153, Office of the Surgeon General, U.S. Army, 19 August 1943, entitled "The Drug Treatment of Malaria, Suppressive and Clinical." By the end of 1943, installations in heavily infested areas had reached their own conclusions on the basis of experience. The view expressed in a special report on malaria in the annual report of the 73d Evacuation Hospital was that all methods in use there were about equally effective in their end results but that quinine and Atabrine used in combination reduced temperature more rapidly than the officially recommended therapy. At the 48th Evacuation Hospital, Lt. Col. (later Col.) Herman A. Lawson, MC, and Maj. John A. Dillon, MC, treated a group of Chinese patients with a somewhat larger total dose of Atabrine than was recommended, but could find no certain advantage. The experience of the theater with the treatment described in Circular Letter No. 153 was summarized in the Essential Technical Medical Data reported to The Surgeon General for June 1944. The general opinion was that only in very sick patients was it necessary to supplement Atabrine with quinine, usually given by injection. Patients with cerebral malaria were sometimes unable to take oral medication. In such cases, before parenteral Atabrine was available, quinine was given intravenously.

During the period covered by Circular Letters Nos. 135, 33, and 153, which included all of 1943 and most of the malarial season of 1944, occasional investigations were made, particularly at the 20th General Hospital, on the effectiveness of drugs or combinations of drugs other than those recommended, and also on the side effects and usefulness of commonly used drugs.

The treatment of relapse in benign tertian malaria with a combination of Atabrine and Mapharsen (oxophenarsine hydrochloride) was studied by Maj. Calvin F. Kay, MC. Relapses occurred in the group so treated as frequently as in those treated with Atabrine alone.

Fraxine, a preparation used by Chinese medical officers and tested at their request, proved of no value in malignant tertian malaria, and its effectiveness in benign tertian malaria was extremely doubtful in view of the apparent tendency of Chinese troops to recover spontaneously.

A special problem with Chinese patients was to keep them in the hospital. As soon as they felt better they left or were taken out by their commanding officers. To circumvent this, Maj. Thomas E. Machella, MC, sought to devise a safe and effective method of giving the total dose of Atabrine within 24 hours. A group of 80 Chinese patients given 0.3 gm. of Atabrine every 3 hours for eight doses, did as well or even better, as regards duration of fever and parasitemia, as compared with patients treated according to Circular Letter No. 153. Because 2 of the 80 patients showed signs of stimulation of the central nervous system, the dosage was reduced to 0.2 gm. every 3 hours for eight doses.

An experimental study by Major Machella failed to demonstrate any effect of a single intravenous infusion of an antimalarial (Atabrine or SN 6,911) upon the ability of the liver to excrete bromsulphalein before, during, and after an attack of malaria. Some patients with cerebral malaria were treated with a single intravenous infusion of Atabrine, the dose varying from 0.6 gm. to 1.0 gm. The patients who received the infusion too rapidly had brief psychotic episodes. Although the number of cases was small, Major Machella felt that Atabrine was at least as effective as quinine, and that 0.8 gm. Atabrine given by slow intravenous drip was an effective method of clearing the blood of parasites.

All three drugs commonly used in the treatment of malaria produced reactions. Plasmochin proved to be particularly toxic in Negroes. Many Negro patients from units working along the Ledo-Burma road were seen at the 73d Evacuation and 20th General Hospitals. A severe type of hemolytic reaction to Plasmochin occurred in approximately 30 patients. One patient was Chinese and the rest were Negroes. All of them developed a moderately severe anemia; in six, the erythrocyte count fell below two million. Because of the frequency and severity of these reactions, administration of this drug was stopped in all hospitals in the Assam-Burma region, and eventually in the theater.

Quinine had long been known to produce toxic effects. Used intravenously in cases of cerebral malaria prior to the advent of parenteral Atabrine, it was generally considered a lifesaving procedure. At the 48th Evacuation Hospital, however, eight Chinese patients died in convulsions shortly after injection of quinine. Although admittedly a cause and effect relationship could not be proved, the clinical impression was so strong that at this hospital any reasonable alternative was regarded as preferable.

All the reactions commonly attributed to Atabrine were seen in this theater, including atypical lichen planus and various other skin reactions, toxic psychoses, and the usual gastrointestinal disturbances. When suppressive treatment with Atabrine was instituted in February 1945, many medical officers were still apprehensive of its supposed toxic potentialities. Many symptoms were attributed to Atabrine without good evidence of a causal relationship, others on a more plausible basis. The Air Transport Command's division surgeon, Col. Edward A. Abbey, MC, and the chief of preventive medicine, Maj. Edgar A. Lawrence, MC, reported on the effects of continued doses (0.1 gm. daily) on the visual acuity of airplane pilots, concluding there was no adverse effect except in rare, highly sensitive individuals. In these, withdrawal of Atabrine resulted in relief of symptoms; readministration of the drug was followed by recurrence, which in turn was relieved by cessation of suppressive therapy.

Various nonspecific therapeutic measures were employed, particularly at the 20th General Hospital, with variable benefit. Transfusions of whole blood were thought to be lifesaving in some cases, especially in those with pulmonary edema. At this hospital an initial spinal tap was considered advisable in all cases. At the 73d Evacuation

Hospital, on the contrary, the reduction of spinal-fluid pressure by lumbar puncture was thought to be appreciably effective only in rare cases. At both hospitals intravenous Adrenalin (epinephrine) was considered of value in some cases, but was not in routine use because of untoward reactions. Sedatives were universally used for excited or convulsive patients, usually Amytal Sodium or paraldehyde given intravenously. Various other measures were tried without any striking benefit. These included oxygen therapy, Benzedrine (racemic desoxy-nor-ephedrine), ephedrine, aminophylline by intravenous and by intracarotid injection, and injection of nitroglycerine into the carotid.

EXPERIENCE IN THE MEDITERRANEAN (FORMERLY NORTH AFRICAN) THEATER OF OPERATIONS

Lt. Col. Harold H. Golz, MC, 182d Station Hospital, and Maj. Phillip B. Bleecker, MC, 225th Station Hospital, collected and compiled extensive data on the epidemiology, clinical and laboratory diagnosis, clinical course, and treatment of malaria in U.S. Army troops in countries bordering the Mediterranean. What follows is in large part taken from the final report on malaria written by Colonel Golz.[4]

Throughout recorded history, malaria played its part in the insidious defeat of armies, and here, in this theater in World War II, it rapidly became the foremost medical problem. The vast majority of American troops who moved into these highly malarious regions had never been exposed to the disease, and the great majority of medical officers had had no experience with it. At that time, the possibilities of drug prophylaxis and suppression were only in process of being elucidated, and mechanical protection from infection in amphibious operations could at best be only a feeble effort. Fortunately, the initial landings were made at a season when the incidence of primary infections was low.

The disease occurred throughout the theater, more intensively in certain regions. In North Africa, the most highly malarious areas were in the neighborhood of Rabat and Port Lyautey in Morocco, the Constantine area in Algeria, and the Tunis-Bizerte-Ferryville area in Tunisia. Sicily had a high rate on the Catania plain and on the southern coastal plain. The entire eastern coastal plain of Corsica was highly malarious, and the malaria rate in civilians of Sardinia was the third highest in the world. A survey of 802 children in Sardinia before World War II showed that 34.2 percent had positive smears, of which 51.4 percent were *P. falciparum* and 43.1 percent were *P. vivax*.

The worst malarial areas in Italy were in the region of Salerno and Paestum, along the Volturno and Garigliano Rivers, about the Pontine Marshes, and around the river mouths on the eastern coast. There was little malaria in southern France, and urban centers such as Florence were free of malaria, although it did approach the municipal limits of Rome and Naples.

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[4] Golz, Harold H.: Human Malaria in the North African and Mediterranean Theaters of Operations, U.S. Army. [Official record.]

Incidence

Based on sample tabulations of individual medical records, there were approximately 81,000 cases (attacks) of known malaria in the U.S. Army in the Mediterranean theater during 1942–45. These cases consisted of new admissions and readmissions as well as admissions for other causes, but in which malaria existed concurrently or developed subsequently (table 54, ch. XIV). There were approximately 28,000 cases of FUO (fever of undetermined origin) recorded on individual medical records in the Mediterranean theater during the war period, and of these, between 5 and 10 percent were probably malaria. Assuming that 7.5 percent, or 2,100 cases, of FUO's were malaria, this number, when added to the approximate 81,000 known malaria cases, produced about 83,000 probable cases of malaria in the Mediterranean theater during 1942–45. By year, this meant that there were less than 1,000 cases in 1942, about 34,000 in 1943, 40,000 in 1944, and 8,000 cases in 1945.

The data on malaria, by month, in the Mediterranean theater for 1942-45 are shown in table 66. The 1942–43 data are based on tabulations of individual medical records and consist of new cases admitted for malaria and new cases in which malaria appeared as a secondary diagnosis. The 1944–45 data are from the statistical health reports and are in terms of total malaria

TABLE 66.—*Malaria cases* [1] *in the Mediterranean (formerly North African) Theater of Operations, U.S. Army, by month, 1942–45*

[Data based on tabulations of individual medical records (1942–43) and statistical health reports (1944–45)]

[Rate expressed as number of cases per annum per 1,000 average strength]

Month	1942 [2]		1943		1944		1945	
	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate
January	-------	-------	517	24. 95	1, 392	29. 11	759	19. 95
February	-------	-------	214	10. 28	2, 214	46. 61	636	15. 98
March	-------	-------	60	2. 24	4, 498	72. 11	988	20. 60
April	-------	-------	86	2. 89	4, 222	80. 24	1, 077	28. 23
May	-------	-------	180	4. 85	3, 022	56. 67	1, 139	31. 20
June	-------	-------	1, 847	47. 82	4, 691	69. 75	1, 002	25. 81
July	-------	-------	4, 806	112. 00	4, 341	81. 26	639	23. 67
August	-------	-------	8, 516	191. 50	4, 897	90. 78	392	15. 32
September	-------	-------	6, 047	129. 78	4, 870	73. 88	111	7. 90
October	-------	-------	6, 235	122. 93	3, 270	60. 96	32	2. 96
November	67	8. 58	2, 550	53. 24	2, 030	38. 04	21	2. 41
December	664	43. 92	1, 753	34. 85	1, 235	25. 48	4	. 88
Total	731	31. 89	32, 811	71. 84	40, 682	61. 67	6, 800	20. 52

[1] The 1942–43 data represent incidence; it consists of new cases admitted for malaria and cases in which malaria appeared as a secondary diagnosis. The 1944–45 data are in terms of total malaria attacks, which is comprised of cases readmitted for malaria as well as new primary and secondary cases.

[2] No troop strength present in the theater before November 1942.

attacks which include readmissions as well as new cases. The statistics enumerate the malaria attacks as they were diagnosed and reported currently and regularly on the statistical health report and may include tentative diagnoses. Such data therefore do not tally identically with those derived from statistical tabulations of individual medical records which are based on final diagnoses. However, they do provide a general basis for epidemiological description of malaria in the Mediterranean theater during World War II. The average length of hospitalization for this disease in 1943 was a fraction less than 17 days, representing a total of about 425,000 man-days lost during the year or the equivalent of the effectiveness of an entire division lost for a month. In 1944 the average period of hospitalization was reduced to 11.8 days but the number of man-days lost for the year was 519,000. In the average hospital, malaria represented 4 to 5 percent of all hospital admissions.

The geographic distribution of the cases broken down into clinical types is shown in table 67. This table shows only 22,936 cases and represents the total experience of 32 hospitals of all types during their entire period of operation in NATOUSA (North African Theater of Operations, U.S. Army) to August 1944. Table 68 shows the incidence of clinical types for the remainder of 1944 and about half of 1945, when the bulk of our troops were in Italy.

In the Sicilian campaign (9 July to 17 August 1943), the loss in fighting effectiveness in the Allied armies was equivalent to two infantry divisions and exceeded the total number of battle casualties by 20 percent. A large number of men also developed the disease while in training in areas of troop concentration in North Africa and were unable to participate in the invasion. The number of troops thus affected was well over a thousand.

The malaria of Sicilian origin made its appearance in the Seventh U.S. Army and British Eighth Army after 7 August 1943 and reached a peak a week later. The rates for these two armies were 425.43 and 420.39, respec-

TABLE 67.—*Experience of 32 hospitals with malaria during the entire period of operation in the Mediterranean (formerly North African) Theater of Operations, U.S. Army, to August 1944, by area*

Area	*Vivax* (tertian) malaria	*Falciparum* (estivo-autumnal) malaria	*Malariae* (quartan) malaria	Mixed-type malaria	Unclassified malaria	Clinical malaria	Total	Percent
Africa	7,068	1,221	94	15	505	983	9,886	43.1
Italy	7,737	507	19	5	449	1,329	10,046	43.8
Sicily	2,428	340	------	32	17	-------	2,817	12.3
Other areas [1]	174	11	2	------	------	-------	187	.8
Total	17,407	2,079	115	52	971	2,312	22,936	100.0
Percent of total	75.9	9.1	0.5	0.2	4.2	10.1		100.0

[1] Pantelleria, France, Corsica, and Sardinia.

TABLE 68.—*Malaria cases discharged from all hospitals in the Mediterranean (formerly North African) Theater of Operations, U.S. Army, from 15 September 1944 to 11 May 1945, inclusive*

Period	*Vivax* malaria		*Falciparum* malaria		Quartan malaria		Mixed or unclassified malaria		Clinical malaria		Total
	New	Old	New	Old	New	Old	New	Old	New	Old	
15 Sept.-27 Oct	1,541	762	76	8	1	2	63	37	112	28	2,630
28 Oct.-8 Dec	1,042	824	448	5	2	----	18	15	152	56	2,162
9 Dec.-12 Jan	414	551	15	7	----	----	3	8	75	46	1,119
13 Jan.-2 Feb	185	304	4	4	----	----	----	9	12	23	541
3 Feb.-2 Mar	190	444	1	3	1	1	1	7	22	22	692
3 Mar.-30 Mar	257	442	2	2	----	----	3	4	18	25	753
31 Mar.-27 Apr	329	434	2	----	2	1	4	5	53	51	881
28 Apr.-11 May	256	281	1	----	----	----	6	6	14	23	587
Total	4,214	4,042	149	29	6	4	98	91	458	274	
	8,256		178		10		189		732		9,365
Percent of total	88.2		1.9		0.1		2.0		7.8		100.0

tively, although in some divisions they were much higher. The incidence in the entire campaign would approximate 400 per 1,000 per annum. Later, strict control measures were adopted. The rates dropped steadily, but it was not so much the control measures that were responsible for the drop in the malarial rates in Sicily in the fall of 1943 as it was the removal of troops from hypermalarious areas and the fact that it was fall of the year.

Several explanatory remarks should be made in referring to table 66: In 1943, the highest rates occurred during the summer months when they were expected. In October 1943, when the bulk of U.S. troops were in North Africa, there was a rise in the rate which was also expected because of the September rains, but this rise did not appear in 1944 when the greater part of U.S. troops were in Italy. The increase in malaria noted in 1943 cannot be attributed to conditions in North Africa. It resulted from conditions existing on the Salerno beachhead during September and had its origin in the sharp increase in cases of malaria in the Fifth U.S. Army during that period. The rates in the winter of 1943 and 1944 were relatively high during the season when few if any primary cases occur and are explained by the relapses of primary infections incurred during the summer and early fall of 1943. The withdrawal of Atabrine suppressive treatment from November 1943 to May 1944 undoubtedly played an important role in these rates. In 1943, the FUO rate was twice as high as that in 1944 because, for various reasons, the effort to make laboratory diagnoses in that year was not as great.

In the summer of 1944, the FUO rate was noticeably high. This can be accounted for in part by the high incidence of pappataci fever from July through September. Many medical officers were unfamiliar with this disease and diagnosed such cases as fever of undetermined origin.

The relatively high rate in August and September 1944, however, has another explanation. For several months prior to the invasion of southern France (15 August), three divisions that had been withdrawn from the Fifth U.S. Army and assigned to the Seventh U.S. Army were staged and trained in a malarial area near Naples. These divisions, classed as noncombat troops, had malarial rates of 130 to 140 per 1,000 per annum while in training.

Hospitalization

Medical battalions.—Through the usual channels of evacuation, a sick soldier reached the clearing station by way of the battalion aid station and the collecting station. At each of these, the need for hospitalization and treatment was evaluated. When the need was recognized, the patient was evacuated to the next medical echelon. Thus, he usually reached the evacuation hospital from the clearing station. At the collecting and clearing stations, facilities for making the diagnosis of malaria on other than clinical grounds were not often available so that the patient ordinarily left the clearing station with a diagnosis of fever of undetermined origin or, occasionally, suspected malaria, without having had specific treatment. Under exceptional circumstances when the military requirement for manpower was pressing, a diagnosis of clinical malaria might be made by the surgeon at the collecting station on the basis of a recent previous attack of malaria, a typical history, and a palpable spleen. If the soldier was only mildly ill, the surgeon might return him to his unit with instructions to remain at rest in his tent for several days, and standard Atabrine treatment was administered under the close supervision of a company aidman. Although this method of management left much to be desired, it resulted in the saving of many man-days that would ordinarily have been lost through evacuation, hospitalization, and the process of return to unit.

Evacuation hospitals.—This type of hospital was the first stop in the chain of evacuation where adequate facilities existed for making a laboratory diagnosis of malaria. These hospitals used the same diagnostic methods as employed in the fixed hospitals of rear echelons—namely, repeated thick smears. (The 15th Evacuation Hospital took three thick and thin smears for routine examination and if these were negative, a fourth was taken 2 hours after the subcutaneous injection of 0.5 cc. of Adrenalin 1:1,000. If the smear following Adrenalin was negative, the diagnosis of clinical malaria was made only if there was a history of recent malaria, a typical clinical picture, and a palpable spleen.) As a result of such careful methods of examination, often done under highly adverse conditions, the diagnosis of clinical malaria was not often made in evacuation hospitals.

Evacuation policies varied widely from time to time and were influenced by (1) the anticipated need for beds, (2) the experience of the corps, army, or base section surgeon, and (3) the professional intelligence of the medical officer who was directly responsible for the administrative phases of evacuation. During the Sicilian campaign of 1943, hundreds of patients suffering from malaria were evacuated from the II Corps area to North Africa because sufficient beds for their care were not available, owing to the fact that the Seventh U.S. Army broke away from its prepared plan of providing hospitalization and did not call for all of their large evacuation hospitals until after the campaign was over. In the fall and early winter of 1943, hundreds of patients ill with malaria were evacuated to hospitals in the Peninsular Base Section because beds for their care were not considered to be available in the Fifth U.S. Army area, although data on the bed status during that period show that rarely after 1 November were there less than 1,500 usable beds in the Fifth U.S. Army area and that generally the figure for empty beds was much greater. With experience, fewer and fewer malarial patients were evacuated. Much unnecessary evacuation of malarial patients with a resultant loss of manpower occurred--both in forward and in rear areas--because many administrative officers in charge of evacuation looked upon patients as "bodies" occupying space without reference to their disease and their ability to return to their units promptly.

When patients were evacuated, they were moved by air, rail, ship, or ambulance to the next echelon hospital, usually the general hospital, although in certain instances they might be sent to a station hospital.

General hospitals.—By the time the malarial patient reached the general hospital, diagnosis had usually been made and treatment started. When the course of treatment was completed, the patient was given such reconditioning as he might require and was then returned to his unit by way of the replacement depot. Most general hospitals made the diagnosis of clinical malaria only in very exceptional circumstances, although they concurred in such a transfer diagnosis when the patient had already been under treatment. When this diagnosis was made initially in these hospitals, it was usually in cases in which, although thick smears were negative, the patient's condition required prompt treatment and his response to specific treatment was typical.

Under certain circumstances, general hospitals received patients directly from command by way of a dispensary. When malaria was suspected in these cases, every effort was expended to make a laboratory diagnosis. At the 12th General Hospital, when the combination of leukopenia, qualitative changes in the lymphocytes of the peripheral blood, and reticulocytosis was found, repeated thick smears were taken without further request from the ward officer.

Another source of admission was in transfers from station hospitals from which the patients were sent as problems in disposition.

It was only in the last half of 1944 that hospitals in this theater reclassified soldiers to limited assignment because of malaria. This reclassification, made but rarely, was usually applied to a combat individual who had been relatively noneffective because of repeated hospitalizations without, however, meeting the criteria for evacuation to the Zone of Interior. Frequently, letters from unit medical officers requesting reclassification accompanied the soldier to the hospital. The purpose was to permit the combat unit to get a more effective replacement and to move the patient to an environment where he was less likely to relapse and could still be of some use to the service.

The theater policy for reclassification to class C (return to the United States) for malarial patients was set forth in Circular Letter No. 21, Office of the Surgeon, Headquarters, NATOUSA, dated 3 April 1944. The criteria for this classification were cachexia, repeated attacks with persistent splenomegaly, refractory anemia, repeated attacks of cerebral malaria, and blackwater fever. This policy did not envisage evacuation to the Zone of Interior for repeated attacks per se. Approximately 1 percent of patients with malaria eventually were sent to the United States for this cause. A review of the records of several general hospitals revealed the following additional causes for C classification:

1. Chronic cachexia with or without persistent splenomegaly and anemia in a patient who had lost 3 months or more from duty in 1 year because of malaria.
2. Proved intolerance to both Atabrine and quinine.
3. Treatment-resistant parasitemia.
4. Psychosis following *falciparum* infections.
5. Repeated attacks of *falciparum* malaria.

Station hospitals.—These hospitals were not normally in the chain of evacuation and for the most part received their patients directly from command by way of dispensaries, although during periods of peak evacuation, the station hospital might supplement the bed capacity of general hospitals. Many cases had a laboratory diagnosis made in the referring dispensary, and when the report of the smear accompanied the patient it was accepted without verification. Other cases arrived with the diagnosis of fever of undetermined origin. Diagnostic methods then employed were the same as those used in the general hospitals, and a diagnosis of clinical malaria was rarely made. For example, in one station hospital, it was resorted to only seven times in more than 800 malaria admissions, and in 6 of these cases, it was the transfer diagnosis of patients already under specific treatment. Treatment methods and criteria for reclassification to limited assignment were the same as those employed in general hospitals. When it was felt that a malaria patient should be evacuated to the Zone of Interior, he was transferred to a general hospital for disposition.

Duration of hospitalization.—From the Machine Records Unit, Allied Force Headquarters, it was determined that the overall average period of

hospitalization for 6,078 cases of malaria in the 8-month period between September 1944 and May 1945 was 14.5 days. This average applied only to cases discharged to general military duty and did not include reclassified cases or cases disposed of by transfer to other hospitals. When calculated for type of hospital the following averages were obtained: (1) Field and evacuation hospitals, 10.4 days; (2) station hospitals, 13.9 days; and (3) general hospitals, 22.6 days.

Laboratory procedures.—In the early days of this theater, the diagnosis "clinical malaria" was made more often than was necessary. Clinicians had no hesitancy in ascribing responsibility for this to the inexperience of laboratory technicians which was undoubtedly a factor, but clinicians should not forget that their own unfamiliarity with the disease was as large a factor, if not larger. After more than 2 years of rich experience with malaria, most hospital clinicians and technicians had become thoroughly acquainted with it. These two groups were mutually helpful in the quest for knowledge of this disease, and certainly much credit for this happy state of affairs can be ascribed to those officers in high echelons of the theater who waged a relentless war against the diagnosis of "clinical malaria." Subsequently, hospital medical officers almost without exception proudly claimed that they rarely if ever made the unsupported diagnosis and they staunchly defended their own technicians as experts in parasite identification. And, indeed, the rank and file of laboratory technicians in the theater had become highly efficient parasitologists; for this, due credit must be given to the training courses for technicians conducted by the malariologists.

A note on technique may not be amiss. All hospitals agreed that a thick-drop blood film was indispensible. In 17 of 20 hospitals visited, thick-drop examination was routine, and several of these hospitals had dispensed with the thin smear entirely, maintaining they could identify the species satisfactorily on the thick drop. In the other three hospitals, the thin smear was examined first, and if negative, the thick drop was examined. The purpose was to save time in diagnosis, but in Italy, where the ratio of *P. vivax* to *P. falciparum* was about 46:1, perhaps such urgency was unwarranted.

For routine work, more than one-third of the hospitals preferred Field's stain, prepared fresh each week, kept cold, and filtered at least twice weekly. Other hospitals invariably used Giemsa stain in preference to Wright's stain.

Many studies were carried out in the laboratories of Army hospitals, which have been described in detail elsewhere (p. 489). Here it may be noted, that certain characteristics formerly though to be limited to *falciparum* infections were not uncommonly found with *P. vivax*; in particular, double-cell infections, double-chromatin dots, and marginal rings.

Treatment

Theater directives.—The history of the treatment of malaria in this theater properly begins with Circular Letter No. 6, Office of the Surgeon,

Headquarters, NATOUSA, dated 10 April 1943, in which the QAP (quinine-Atabrine-Plasmochin) treatment is recommended; that is, quinine 0.67 gm. three times a day for 2 or 3 days to control parasitemia, followed by Atabrine 0.1 gm. three times a day for 5 days followed by a 2-day rest period, and then 0.1 gm. of Plasmochin two or three times a day for 5 days. Circular Letter No. 32, Office of the Surgeon, Headquarters, NATOUSA, 3 September 1943, amended Circular Letter No. 6, eliminating Plasmochin from the schedule and also recommending, as an alternative, Atabrine alone, 0.2 gm. three times a day for 5 days. Finally, on 14 September 1943, Circular Letter No. 34, Office of the Surgeon, Headquarters, NATOUSA, advocated the Atabrine schedule: 0.2 gm. of the drug every 6 hours for five doses followed by 0.1 gm. three times a day for 6 days. Circular Letter No. 10, Office of the Surgeon, Headquarters, NATOUSA, dated 15 February 1944, recommended that for third and subsequent relapses quinine be used in a dosage of 1.0 gm. three times a day for 3 days and then 0.3 gm. three times a day for 10 days. Circular Letter No. 41, Office of the Surgeon, Headquarters, NATOUSA, dated 29 July 1944, rescinded Circular Letter No. 10 in view of the fact that the use of quinine in the therapy of relapsing malaria had shown no advantages over the use of Atabrine.

Atabrine.—This therapeutic Atabrine dosage scheme was found to be safe, effective, and productive of results equally as good as those obtained with quinine. Formerly, it had been observed that Atabrine did not effect a temperature drop as promptly as did quinine. At that time, it was not the practice to administer loading doses of Atabrine during the first day or two of treatment. This objection was largely eliminated after it was found that the plasma concentration of the drug was a measure of its therapeutic effectiveness and that effective levels were more rapidly attained when larger doses were given at the start of a therapeutic regimen.

It was the experience of all the medical officers of the Mediterranean theater that many soldiers said they were intolerant of Atabrine, but when the drug was given in either suppressive or therapeutic doses, no such intolerance was demonstrated. Toxic reactions from therapeutic Atabrine were extremely rare. There were probably few if any medical officers in this theater who were not finally convinced that Atabrine was at least as effective and safe as quinine. This attitude represented a complete reversal of opinion within 2 years and, as such, was an eloquent testimonial to the value of the drug. When Atabrine was introduced as a suppressant in doses of 0.2 gm. twice weekly 2 years before, there was such an explosive outbreak of gastrointestinal symptoms that the drug fell into some measure of disrepute. Medical officers were wary and suspicious of it, and only its continued use at the insistence of higher authority served to dispel these fears. A few officers still remained somewhat reluctant to accept Atabrine as the drug of choice. They were mainly physicians who had become thoroughly indoctrinated with the virtues of quinine when it was the only efficient antimalarial available.

The chief remaining differences of opinion regarding the effectiveness of the two drugs were concerned with the speed of action in bringing the temperature into the normal zone. When Atabrine was given as directed in Circular Letter No. 34 and quinine as directed in Circular Letter No. 10, many officers thought that quinine brought the temperature to normal 24 to 48 hours sooner than did Atabrine and that in most cases patients did not have another chill after quinine was started, whereas most had one additional paroxysm after Atabrine. A smaller group of officers could observe no difference in this respect between the two drugs, and a small minority thought that Atabrine produced faster results. Obviously, these differences of opinion were largely due to the fact that they were based upon clinical impressions. The only factual data on the subject were gathered by Capt. (later Maj.) Franklin K. Paddock, MC, of the 33d General Hospital on 28 cases treated with quinine and 24 cases treated with Atabrine, in such dosage as has been described. His results are summarized in table 69 and show that there was little difference between the two drugs.

TABLE 69.—*Results of study of duration of fever after start of treatment in 28 quinine-treated cases and 24 Atabrine-treated cases of malaria*

Duration of fever (days)	Quinine		Atabrine	
	Number	Percent	Number	Percent
1	14	85. 7	24	100. 0
2	21	75. 0	22	91. 7
3	13	46. 4	7	29. 2
4	2	7. 1	2	8. 3

In many hospitals, 0.4 gm. Atabrine by intramuscular injection was substituted for the initial dose of 0.2 gm. Atabrine given orally. Officers who used this modification of the routine plan were enthusiastic over the results. There were no toxic effects; temperatures fell to normal within 24 hours; there was no secondary rise in temperature and no additional paroxysms; and convalescence was quicker. Several other hospitals initiated treatment with 0.2 gm. given intramuscularly. The results were not as good as with the larger dose. The 118th Station Hospital gave 0.4 gm. Atabrine orally in one dose and followed it with 0.1 gm. three times daily. Results were said to be comparable with those obtained from the larger of the doses given intramuscularly.

Plasmochin.—The drug was dropped from the therapeutic armamentarium early because no peculiarly beneficial effect was ascribed to it and because of the narrow margin of safety between therapeutic and toxic doses.

Quinine.—For reasons of supply, its use was limited. Patients were occasionally seen who failed to respond to quinine given orally and in whom no

trace of the drug could be found in the urine. In certain types of cases, it was freely used intravenously, in all instances well diluted and given slowly. Circular letters directed that quinine should be administered in at least 300 cc. of normal saline or glucose and saline. Reactions other than mild cinchonism were not seen. In cerebral malaria, this was the routine method of treatment. It was usually given in infections with *P. falciparum* when patients were vomiting. One hospital gave at least one dose of quinine intravenously in all *falciparum* infections. The dose employed was almost invariably 10 gr., and it was repeated at 6- to 8-hour intervals when necessary.

Sulfonamides.—Occasionally, a misdiagnosed case of malaria was treated with one of the sulfonamide drugs. It was observed that the drug, usually sulfadiazine, did suppress clinical symptoms and parasitemia. A few reports were received indicating that sulfadiazine in full therapeutic doses might possess some merit in the treatment of *falciparum* gametocytemia resistant to Atabrine and quinine.

Sontoquine.—A limited supply of Sontoquine bisulfate and Sontoquine naphtholate was received in the theater and divided between the 225th and 182d Station Hospitals. It was planned that each hospital should treat equal numbers of malaria cases with each of the two drugs and that a third group should be treated with Atabrine for comparison. Unfortunately, the experiments were undertaken at a season when the malaria rate was the lowest in theater history, and during the period of study both hospitals were moved to other locations in Italy. Consequently, a total of only 14 cases were studied in the two hospitals. Of these, eight patients received Sontoquine and six patients received Atabrine. The dose of all three drugs was 0.2 gm. every 6 hours for five doses and then 0.1 gm. three times a day for 6 days. There was no difference noted between the two salts of Sontoquine and no difference between these drugs and Atabrine. Temperatures returned to normal and blood smears were negative within 48 hours in the patients treated with Sontoquine and in all but one of the patients treated with Atabrine. This one patient had fever and positive smears until the fifth day of treatment. No sign or symptom of intolerance to Sontoquine was noted, and repeated blood counts and urinalyses failed to show any ill effects whatsoever. It was planned to continue this study.

Iron.—Routine use of iron in all cases of malaria in some hospitals was thought to speed convalescence.

Other measures.—Intravenous glucose and saline were freely used to combat dehydration. In *vivax* cases with vomiting, the fluids often seemed to allay this symptom so that patients could retain oral therapy. One hospital reported that a single dose of morphine had a similar effect.

In patients gravely ill with *falciparum* infections, repeated infusions of plasma and whole blood were frequently employed. Several medical officers felt that these measures were frequently lifesaving.

Treatment To Reduce Relapse Rate

Throughout the entire history of the theater, officers were searching for a therapeutic regimen that would reduce the relapse rate in *vivax* infections. The 7th Station Hospital reported that relapse after Atabrine treatment appeared to be considerably delayed and that recurrence frequently followed quinine treatment within a matter of days or weeks.

Many different dosage schedules and combinations of Atabrine, quinine, and Plasmochin were used in the various hospitals and some of these programs required weeks of hospitalization. The criticism common to all of these studies was that they were done in only a very small series of cases; they were not controlled, and followup studies were either inadequate or completely lacking. It is perhaps significant that not a single officer was found who had any faith whatsoever in any of these or other plans of treatment designed to prevent relapses. For the sake of interest and completeness, several of these plans will be noted.

One hospital supplemented routine Atabrine or quinine treatment with a modified Ascoli treatment plan. Adrenalin was given intravenously in graduated doses beginning with 0.01 mg. and increasing to 0.1 mg. or to tolerance. Eight patients received this treatment daily for 15 days and four received it twice daily for 10 days.

Another hospital gave quinine intravenously with Adrenalin three times daily for 7 days. Another hospital gave 0.2 gm. Atabrine every 6 hours intramuscularly followed by 0.2 gm. twice daily by the same route for 6 days. The local effects were said to have been disagreeable.

Still another hospital gave a routine course of quinine followed by a routine course of Atabrine followed by four weekly doses of Mapharsen. Another hospital gave a routine course of Atabrine, followed by a routine course of quinine, followed by a routine course of Atabrine. On the first day of treatment the patient received 0.4 gm. bismuth subsalicylate, intramuscularly, and on the 7th, 14th, and 21st days, 0.2 gm. In addition he received 60 mg. of Mapharsen twice weekly for six doses.

In many of the above instances patients relapsed within a month or two after completion of treatment.

Capt. (later Maj.) John C. Ransmeier, MC, of the 300th General Hospital treated three cases of relapsing *vivax* malaria with Fuadin (stibophen) (one with quinine as well, two with Fuadin only) reasoning that its penetration into the cells of the reticuloendothelial system might be effective. One patient received 6 daily doses of 5 cc. intramuscularly, another 10 cc. doses daily, and the third 10 doses of 5 cc. each at 24- to 48-hour intervals. The patient who received quinine as well was followed for only 1 month, during which he was well. In the second patient, the temperature became normal within 48 hours and parasites disappeared from the peripheral blood within 96 hours. He relapsed on the 13th day after completing treatment. The third patient became afebrile within 72 hours. At the conclusion of treatment parasites were absent from the peripheral blood for only 72 hours. Clinical relapse occurred in the ninth posttreatment day. Mild neutropenia was observed in all three cases.

As a result of experiences such as those cited, few medical officers in this theater believed that current methods of treatment could do more than suppress symptoms and parasitemia in *vivax* malaria. In another theater, prolonged experience suggested that Atabrine therapy not only was effective in

suppressing relapsing malaria but, if continued long enough, might ultimately cure it (p. 497). There is no indication in Colonel Golz's report that such consistently long-sustained therapy was ever carried through in the Mediterranean theater where, indeed, conditions were lacking for such continuous observations on identical groups of men as were possible in the Pacific area. The desideratum was a method of treatment that would obviate relapses. The British thought they had achieved this goal, or come near it, by their use of Plasmochin in conjunction with quinine. U.S. Army medical officers had early discarded Plasmochin, finding it of no particular merit as used by them, and very toxic, especially in Negro troops. Our achievement was rather in the increasingly more efficient use of Atabrine. Both lines of thought were fruitful and, during and since World War II, have been carried to more effective therapy and new drugs.

Results of Treatment

Mortality.—One measure of the effectiveness of treatment is the death rate which in the Mediterranean, as in all theaters, was extraordinarily low. In the entire history of the theater, there were approximately 62,000 definitely diagnosed new cases of malaria in U.S. Army troops. According to individual medical records for 1942–45, there were 57 deaths due to malaria among cases originating in the Mediterranean theater. There were 3 deaths in 1942, 40 in 1943, 13 in 1944, and 1 in 1945. After an extensive search, Colonel Golz discovered only 11 deaths that actually occurred in the Mediterranean theater. Of 8 deaths ascribed to malaria on clinical grounds in official records for 1944, post mortem studies showed that death was due to other causes in 5 (1 Hodgkin's disease, 1 brain tumor, 1 infectious hepatitis, 1 hemorrhagic bronchopneumonia, and 1 "cause undetermined but not malaria"). By any calculation, the mortality was surprisingly low.

There are several reasons for this. Table 67 shows that in Italy the incidence of infection caused by *P. falciparum* was low. Other factors were Atabrine suppressive treatment (curing many *falciparum* infections) and the excellent distribution and the high caliber of medical care available to U.S. troops.

Morbidity.—The malaria relapse rate was 28 percent in the Mediterranean theater and 23 percent in the Pacific areas. These figures are gross figures in that they have not been adjusted to take into account evacuation, death, or transfer of cases. The figures merely reflect a ratio of readmissions to new admissions.

Several attempts were made to assay the dimensions of the problem by indirect means. Colonel Golz, on the basis of data shown in tables 70 and 71, concluded by one line of reasoning that, of any group of primary malaria cases, 30.6 percent might be expected to relapse at least once, with the average number of relapses being 2.08 for the group. He also cited Lt. Col. (later

Col.) James B. McLester, MC, of the 17th General Hospital who, using the same data and some of his own, made a somewhat different approach. Of a group of cases followed from 1 to 10 months, 30.5 percent relapsed. Over one-half of the relapses during the first 9 months occurred in the first 2 months and another quarter, in the next 2 months. Since after 6 months, the monthly rate remained between 1 and 2 percent, it seemed probable that the relapse rate would be found to be between 50 and 60 percent if the followup were more complete and continued longer. Other data, more extensive numerically, derived from 27 hospitals by questionnaire by the malariologist of NATOUSA, suggested, by several lines of reasoning, a relapse rate of about 50 to 55 percent.

TABLE 70.—*Incidence of attacks of malaria reported by 27 hospitals in the Mediterranean (formerly North African) Theater of Operations, U.S. Army*

Number and type of hospitals reporting	Primary		Relapses		Total
	Number	Percent	Number	Percent	
1 field	33	11.3	258	88.7	291
1 evacuation	1,525	83.5	301	16.5	1,826
2 convalescent	55	34.0	107	66.0	162
16 station	5,467	61.1	3,479	38.9	8,946
7 general	1,492	49.6	1,516	50.4	3,008
Total	8,572	60.2	5,661	39.8	14,233

TABLE 71.—*Incidence of relapses due to malaria reported by 18 hospitals in the Mediterranean (formerly North African) Theater of Operations, U.S. Army*

Number and type of hospitals reporting[1]	Number of relapses											Total cases
	1	2	3	4	5	6	7	8	9	10	11	
1 evacuation	184	36	28	29	9	4	7	0	2	2	0	301
1 convalescent	14	15	14	4	3	0	1	2	0	0	0	53
10 station	934	496	267	137	69	32	21	15	6	3	4	1,984
6 general	553	230	126	97	57	43	40	14	8	2	4	1,174
Total	1,685	777	435	267	138	79	69	31	16	7	8	3,512
Percent of total	48.0	22.1	12.4	7.6	3.9	2.2	2.0	0.9	0.5	0.2	0.2	100

[1] Data not available from field hospitals.

Colonel McLester stressed the obstacles to statistical accuracy. In the Mediterranean theater, the number and composition of troops were constantly changing with the tactical situation, and the population at the time of recurrence might be very different in size from the population at the time of pri-

mary attack. Fresh troops might come in who had not previously been exposed to malaria and might have time for only one attack. Soldiers who had had a primary attack might be evacuated, or killed, or transferred to another theater before relapse could develop. Furthermore, in an attempted follow-up of patients who had been treated in the 17th General Hospital, gross errors were found in their medical histories. Also, the record was regarded with suspicion when a patient, known to have had an attack with *P. falciparum*, was reported as having relapse with *P. vivax*.[5]

Table 72 will show that the percentage of cases transferred to the Zone of Interior is not a valid figure for the malaria question as a whole. Many of the admissions to general hospitals were transferred from other hospitals, and with few exceptions only general hospitals had the power to transfer cases to the Zone of Interior.

Many of the cases found in general hospitals had been transferred there by other hospitals specifically for Zone of Interior disposition because of repeated recurrences. Nevertheless, a study was undertaken at the 182d Station Hospital to determine the final disposition of its malaria cases: 757 cases were investigated, of which 437 were recurrent and 320 were primary. Of these, 103 cases were transferred to other hospitals for reasons other than malaria and could not be traced as to disposition. Of the remaining 654, those who were transferred were satisfactorily traced. The result of this study showed that 641 went to general military service, 5 went to limited assignment, and 8 (1.22 percent) were recommended for evacuation to the Zone of Interior by a general hospital.

TABLE 72.—*Malaria patients evacuated to the Zone of Interior from the Mediterranean (formerly North African) Theater of Operations, U.S. Army, 25 hospitals reporting*

Number and type of hospitals reporting	Total cases	Number evacuated	Percent
18 station	10, 604	28	0. 26
7 general	3, 185	250	7. 85
Total	13, 789	278	2. 02

[5] Although complete and accurate statistics on the incidence of relapse are not available from any theater, similar relapse rates for Mediterranean strains (approximately 30 percent) were found elsewhere in this theater and also in the Zone of Interior during periods of 120 days following treatment with various antimalarials. Relapse rates were much higher with Pacific strains during like observation periods of 120 days, being approximately 80 percent in one study and 80 to 90 percent in another. It should be noted, however, that a very much higher percentage of relapses of Pacific origin will fall within the 120-day period (75 percent occurring within the first 60 days in one study). With the Mediterranean strains, there is a longer average interval to the first relapse (150 to 200 days). Even when this is taken into account, the estimated rate of 50 to 60 percent remains appreciably lower for the Mediterranean strains of *P. vivax*.

Modifications of relapse rates by the treatment preceding the observation periods were not such as to invalidate these calculations, except when Plasmochin was used in conjunction with quinine. In extensive comparisons, the majority of relapses occurred within the first month after treatment with quinine or totaquine and within 3 months after quinacrine or chloroquine; that is, well within the span of 120 days.—P. H. L.

Machine records data concerning cases sent to the Zone of Interior are available for the period 15 September 1944 to 6 April 1945. During this time, 8,055 cases of malaria were disposed of and, of these, 90 cases (1.1 percent) were returned to the Zone of Interior for this cause. An additional 36 cases were found with a secondary diagnosis and the available records were not clear as to which diagnosis was responsible for the evacuation. If these two groups are combined, the total number of cases is 126 or 1.6 percent.

Case Histories

In the 13 case histories[6] which follow, examples of particular problems —most of them exceptional, some more typical—are described briefly. Included are eight fatalities.

Skin lesions

Herpes labialis occurred in some cases, and occasionally urticaria, which was usually transitory. Urticaria had been seen more often in the early days of the theater, when quinine therapy was still popular. Colonel Golz reported an interesting case, summarized in case 1. Four hospitals reported seven cases of purpura simplex, beginning shortly after or concomitantly with the clinical onset, and clearing completely soon after the start of antimalarial treatment; in four cases this was associated with *vivax* infections, in three, with *falciparum* infections. One hospital reported 10 cases of erythema multiforme.

Case 1.—In one unusual case, the maturation of each cycle of parasites was accompanied by a severe attack of generalized urticaria and angioneurotic edema of about 12 hours' duration. These attacks occurred three times at 48-hour intervals without any sign or symptom to suggest malaria. There was no elevation of temperature. With the fourth such attack the patient had his first chill and rise in temperature. *P. vivax* was found in his blood. Atabrine treatment resulted in prompt cessation of his hives and he had no further chill or fever. During the 4 months following his discharge from the 182d Station Hospital he had five relapses for which he was admitted to other hospitals, and in each relapse the same train of events occurred. He was then evacuated to the Zone of Interior.

Blackwater fever

Four cases were reported in the Mediterranean theater. Case abstracts of two of these patients are appended, one of whom died. Available data on the third patient were so meager as to raise the question of diagnostic accuracy. Records of the fourth were not available.

Case 2.—The soldier was admitted to the 33d General Hospital with a history of chills, jaundice, and dark urine for 4 days. The record did not state whether he had previously had malaria. Prior to admission he had no treatment. On the day of admission he was stuporous and icteric but malaria smears were negative and the leukocyte count

[6] In another theater, however, under more favorable conditions for prolonged observations on the same body of men, there was shown a reversal of species incidence from 55 percent *P. falciparum*, 24 percent *P. vivax* during an epidemic in a malarious environment, to zero percent *P. falciparum*, 99 percent *P. vivax*, after the troops were removed to a nonmalarious environment.—P. H. L.

was 4,700. On the second hospital day trophozoites of *P. falciparum* were found in the blood. The urine was negative except for a trace of albumin. On the second and third days he was given 2.7 gm. of quinine orally and 1.3 gm. intravenously. On the third day the red blood cell count was 4,330,000, the hemoglobin 13.0 gm., and the leukocyte count 5,300. On the fourth day the urine became reddish brown in color, showed 3+ albumin and was positive to test for occult blood. The red blood cell count had dropped to 3,060,000 and the hemoglobin to 11.5 gm. per 100 cc. Trophozoites of *P. falciparum* were still present in the blood. The blood nonprotein nitrogen was 37.5 mg. percent and the icteric index, 9 units. Quinine treatment was stopped; Atabrine, given orally, was started cautiously; and the patient was given a transfusion of 500 cc. of whole blood. On the fifth day he was much improved; the urine was negative; the red blood cell count, 3,780,000; the hemoglobin, 12.0 gm. per 100 cc.; and gametocytes of *P. falciparum* were present on blood smear. The Atabrine dosage was then increased. Thereafter the course on full doses of Atabrine was uneventful. The urine remained normal although the anemia persisted at a level of about 3,500,000 red cells per cu. mm. Gametocytes of *P. falciparum* were found on the smear daily until the day after Atabrine was stopped.

Case 3.—A 32-year-old soldier was admitted to a station hospital in August 1943 complaining of chills, fever, and general malaise for 4 days. He stated that he had had malaria several years previously in the United States. He also stated that he had been taking Atabrine in suppressive doses regularly. Physical examination revealed nothing of note. Blood smear was positive for *P. falciparum*. He was given 10 gr. of quinine three times daily by mouth. On the second day his general condition had deteriorated and quinine was increased to four times daily. Physical and X-ray signs of bronchopneumonia developed on the third day. On the fourth day the urine became dark brown and gave a strongly positive test for blood. The hemoglobin fell from 13.0 gm. in the morning to 10.5 gm. in the afternoon. The blood nonprotein nitrogen began to rise. He was given a transfusion of whole blood and an intravenous infusion of sodium bicarbonate solution. This treatment was repeated on the fifth day. The course, however, had been progressively unfavorable and he died on the fifth hospital day with a clinical diagnosis of blackwater fever. Autopsy confirmed the cause of death as malaria.

Vague symptomatology

Every hospital representative interviewed in this theater reported occasionally seeing patients who complained of vague symptoms of fatigue, headache, and malaise; whose temperatures remained perfectly normal, and whose blood smears were positive for *vivax* trophozoites. Asymptomatic carriers of *falciparum* gametocytes were relatively more common. Not infrequently met were cases of proved malaria with recent histories of one or more hospitalizations for fever of undetermined origin, with spontaneous remission. It is highly probable that these previous febrile episodes were due to malarial activity.

Case 4.—A soldier without a previous history of malaria was admitted to a station hospital with the admitting diagnosis from his dispensary as "Vague complaints—nervous." The hospital history indicated that he had had a poor appetite, general malaise, and chilly sensations at night for a week. During the first 24 hours in the hospital his temperature remained normal and he showed what were interpreted as signs of an anxiety neurosis. On the evening of the second day in the hospital, the patient had a chill, his temperature rose sharply and he became irrational, confused, and restless. Examination of the blood showed a marked anemia, leukocytosis of 14,000 and a heavy infestation of the red blood cells with *P. falciparum*. In spite of 5 gr. of quinine intra-

venously every 6 hours and four whole blood transfusions of 500 cc. each, his condition gradually deteriorated. He lapsed into coma on the third hospital day and died on the fifth.

Fever

In approximately 75 percent of *vivax* infections, the typical intermittent temperature graph with quotidian or tertian paroxysms was seen. The relatively high percentage of remittent fever (25 percent) may be ascribed to the prompt institution of specific treatment. The majority of *falciparum* infections exhibited remittent fever without frank paroxysms.

Some cases were without fever through all or a large part of their clinical course.

Case 5.—A soldier was admitted to a station hospital with a history of having had chills and fever, nausea and vomiting for a week. On admission jaundice was observed and the liver was palpated three fingerbreadths below the costal margin. He was afebrile and malaria was not suspected. Two days after admission the patient became stuporous. His red blood cell count was 2,700,000, his leukocyte count 40,000, blood nonprotein nitrogen 99 mg. percent, and his blood smear was positive for *P. falciparum*. Despite vigorous treatment with oral and parenteral quinine, the patient died on the third hospital day, having remained afebrile throughout.

Liver and spleen

Hepatomegaly of mild degree was associated with malaria in about 15 or 20 percent of cases. Minimal scleral icterus was seen in less than 5 percent and was thought to be an expression of the blood destructive process that accompanies malaria. Definite jaundice was occasionally seen concurrently with malaria and was thought to be due to complicating infectious hepatitis. Definite jaundice due to malaria did occur in blackwater fever and moribund cases. The term "malarial hepatitis" was freely and glibly used in this theater, but no evidence was adduced to show that such a condition existed. Pathologists found no parenchymal lesion; liver function tests showed only transitory changes, and enlargement of the liver was usually only transitory.

The spleen was often found palpably enlarged during the second week of the acute attack. It was usually soft and tender in the acute stages, and was firm and not tender in the chronic stages. Reports from various hospitals in this theater varied widely as to the incidence of palpable spleens. The acute splenic tumor usually subsided rapidly after antimalarial therapy. Persistent enlargement usually signified a chronic latent infection; many of the cases that had frequent relapses had a chronic splenomegaly. In one case, a ruptured spleen was found at autopsy.

Case 6.—A soldier was admitted to a station hospital in a moribund condition. He was reported to have fainted shortly before admission and on recovering consciousness complained of substernal pain and vomiting. He denied any injury. In the emergency room he showed extreme pallor, air hunger, and restlessness. His pulse was imperceptible. The abdomen was not distended nor tender. A blood smear showed 4 percent parasitization of the red cells with *P. vivax*. Plasma was administered as an emergency measure, but the patient ceased breathing while the plasma was being given. At autopsy the peritoneal cavity was found to be filled with blood and a 4 cm. tear was noted in

the spleen. The pathological diagnosis was splenomegaly due to *vivax* infection, and spontaneous rupture of the spleen.

Gastrointestinal symptoms

Vomiting, occurring in about 20 percent of *vivax* infections, was usually not severe and was associated only with the paroxysms; in *falciparum* infections, it tended to be more severe and persistent and was one of the frequent indications of the cerebral syndrome.

Abdominal pain was very common. Most frequent was an achy pain high in the left upper quadrant, sometimes radiating to the left lower chest and often aggravated by respiratory excursions. Infrequent cases were seen simulating acute surgical emergencies. Two in which laparotomy was performed are described:

Case 7.—A soldier was admitted to an evacuation hospital with a history suggestive of a ruptured abdominal viscus. There was boardlike rigidity of the abdominal muscles, and the leukocyte count was 14,000. Exploratory laparotomy revealed nothing abnormal. Subsequently *P. falciparum* was discovered in the peripheral blood. Antimalarial therapy produced complete recovery.

Case 8.—A soldier was admitted to a station hospital with a diagnosis of acute appendicitis, having experienced 24 hours previously the onset of generalized cramping abdominal pain, which subsequently localized in the right lower quadrant. There was nausea but no vomiting or disturbance of bowel habit. There was no history of malaria. The temperature was 102.8° F. and the leukocyte count 5,900. Marked tenderness was noted in the right lower quadrant on direct palpation and on rectal examination. Emergency appendectomy was performed but a normal appendix was removed. The postoperative course for 2 weeks was complicated by intermittent fever of 100° or 102° F. exhibiting a tertian periodicity. (On one occasion he had a chill and a temperature rise to 105° F.) Repeated malaria smears were negative. On the 19th postoperative day *P. vivax* was found. Antimalarial therapy resulted in disappearance of all signs and symptoms.

Generalized aching or cramping abdominal pain was occasionally a complaint, especially in patients with diarrhea. It was usually of mild degree, occasionally more severe, and occurred in about 10 percent of infections with *P. vivax*. In malignant tertian malaria, diarrhea was not more common but was often more severe, at times dysenteric. The stools in such cases sometimes contained red blood cells but never pus, parasites, or pathogenic bacteria. A brief description of a fatal case follows.

Case 9.—A 24-year-old soldier was admitted to a station hospital in October 1943 complaining of severe diarrhea of 5 days' duration. The diarrhea was accompanied by severe abdominal cramps and grossly bloody stools. He had had one chill prior to admission. There was no previous history of malaria but the soldier had fought through the Sicilian campaign several months previously. On examination he was found to be in shock. The pulse was almost imperceptible, blood pressure was 70 systolic and 60 diastolic, and temperature 97° F. The abdomen was rigid, leukocyte count was 25,000 and the red blood cell count was below 3 million. The stools contained dark blood and blood smears were positive for *P. falciparum*. The surgical consultant felt that there was no indication for surgical intervention. On the first hospital day he was given 10 gr. of quinine intravenously, a transfusion of one liter of citrated blood and apparently adequate amounts of physiological saline solution intravenously. Oral quinine therapy

was started. On the second day he was markedly improved. Diarrhea and vomiting ceased; temperature rose to 101° F. and the systolic blood pressure to 110. Oral quinine three times daily was continued. On the third day he suddenly went into a state of peripheral circulatory collapse and promptly died. Autopsy showed an extensive hemorrhagic enterocolitis. Malaria parasites were found in sections of the intestinal tract and the heart showed numerous areas of focal necrosis. No notable changes were found in the brain.

The cerebral syndrome

Of the 57 deaths due to malaria in the Mediterranean theater during 1942–45 (p. 514), 14 were ascribed to *vivax* malaria, 27 to *falciparum* malaria, and 16 to "other or unclassified malaria" (the "other malaria" excluding quartan malaria and mixed malaria infections). In the 11 deaths reported by Colonel Golz, 10 were due to malignant tertian malaria, and of these, 8 were caused by the cerebral form of the disease. All eight cases illustrated the grave danger attendant upon failure, for whatever cause, to initiate vigorous treatment early.

Case 10.—A soldier was admitted to an evacuation hospital with a history of chills and fever for 4 days. There was no past history of malaria. On the day before admission he had a temperature of 104.4° F. with pain in the left upper quadrant, and smears were positive for *P. falciparum*. He was given 0.2 gm. of Atabrine every 6 hours orally. On admission his temperature was 98.8° F. and his general condition seemed to be fair. Blood counts showed a marked anemia and smears showed all stages of *P. falciparum*. Spinal fluid was negative except for increased pressure. On the second hospital day he suddenly became stuporous, psychotic, and could not be aroused. There was only a slight pupillary reaction and his neck was rigid. On this day the patient received a total of 3.3 gm. of quinine intravenously. In spite of this he developed tonic convulsions and died. Blood quinine level was 7.1 mg. per liter.

Case 11.—A 45-year-old soldier was admitted to a station hospital in the spring of 1943 in a marked state of mental confusion and delirium. Because of his mental state no history could be obtained. Persistent vomiting was present. Red blood cell count was 2,000,000 and leukocyte count 12,000. Diagnosis was made on the second day with the identification of *P. falciparum* in the peripheral blood. Ten grains of quinine were given orally three times daily. However, vomiting persisted. On the fourth day 10 gr. of quinine intravenously every 8 hours was instituted, and the patient received this medication four times. He was also given two whole blood transfusions. He lapsed into coma in spite of this treatment and died on the fifth day. Autopsy report was not available.

Case 12.—A soldier was admitted to a station hospital in a comatose state. Signs of lobar pneumonia were present. There was marked anemia, and blood smears were positive for *P. falciparum*. In spite of treatment with sulfadiazine, intravenous quinine, whole blood transfusions, and oxygen, the patient died on the third hospital day. Death was ascribed clinically to cerebral malaria. Autopsy showed lobar pneumonia and numerous malaria parasites in the brain, heart, and muscles.

The incidence of this ill-defined syndrome varied widely among the hospital representatives questioned although none declared it to be common. Restricted to cases showing one or more of such signs as coma, meningismus, convulsions, persistent delirium, and well-defined neurological signs, 144 cases were reported due to *P. falciparum* and 19 due to *P. vivax*. This did not

represent total theater experience, since it was not possible to survey all of the hospitals in the theater.

Of the eight deaths in this theater due to cerebral malaria, all were *falciparum* infections. The modern concept of the pathological physiology of cerebral malaria permits a reasonable doubt as to its occurrence in *vivax* infections. In only 1 of the 19 cases so reported was the record available for analysis, and in this case the accuracy of the diagnosis was questionable. A summary follows.

Case 13.—The patient became ill 6 October 1944 with nausea and some vomiting. Began "shaking." No further coherent story could be elicited. Temperature was 97° F., pulse 104, and respiration 24. There were no abnormal findings. The battalion surgeon who sent the patient to the station hospital on 7 October, suspected malaria. Temperature was 100.2° F. at time of onset.

The patient was semicomatose on 8 October 1944. Lumbar puncture was done on the same day. Pressure was elevated. The first tube contained red cells; the second was crystal clear. There were 84 cells, 30 polymorphonuclears, and 58 lymphocytes. The examining medical officer was not certain that the patient had meningitis. Lymphocytic choriomeningitis or encephalitis was considered. The patient had four generalized convulsions on 11 October and was transferred on that date in deep coma to a general hospital with the diagnosis of epilepsy. On admission considerable motor unrest was noted but no movements of right side. Examination was difficult but did show bilateral ankle clonus and Babinski's and Oppenheim's signs. Abdominal reflexes were absent. Right side of face did not move as well as left; slight internal squint, right eye. Pendular nystagmus, on looking ahead, changed to definite slow vestibular variety on looking to right. Conjugate movements of eyes were preserved; pupils dilated, reacted poorly to light; fundi normal. Patient gave no response to painful stimuli. Definite meningitis neck with direct Brudzinski's sign and bilateral Kernig's sign. Temperature was 102.2° F., pulse 96, respiration 22, and blood pressure 126 systolic and 80 diastolic.

The picture was that of an acute meningoencephalitis. How many of the focal signs were due to the illness per se and how many a product of the postconvulsive state could not then be determined.

Spinal puncture yielded clear fluid; 280 mm. of water pressure; normal dynamics; 4 white blood cells (lymphocytes); sugar, 100 mg. percent; chlorides, 733 mg. percent; globulin, negative. Total protein, 22 mg. percent. Kahn negative. Gold curve, 1,111,000,000. Subsequent smear, culture, and pellicle studies were negative.

12 October 1944: Temperature dropped to normal. Patient responded to questions but was confused much of the time. Neurological signs persisted.

13 October 1944: Spinal fluid examination showed: 260 mm. of water pressure; clear; pressure dropped to 70 mm. of water after removal of 30 cc. of fluid; 5 white blood cells (lymphocytes); sugar, 62 mg. percent (simultaneous blood sugar, 84 mg. percent); chlorides, 759 mg. percent; globulin, negative; total protein, 24 mg. percent. Smear and subsequent culture, negative. Generalized convulsion; then Jacksonian fit of right side. "Status" aborted with intravenous Amytal Sodium.

14 October 1944: Suspect right homonymous hemianopsia (transient). Periods of delirium and hallucinations. Afebrile.

16 October 1944: Two attacks of furor (equivalents). Was being given luminal (phenobarbital). Bromides added.

17 October 1944: Today patient has left homonymous hemianopsia. No astereognosis. Some tendency toward preservation. Meningeal signs persist.

18 October to 23 October 1944: Essentially the same. Some confusion. Hemianopsia (left) persists.

24 October 1944: Temperature to 101.8° F. Malaria smear positive for tertian parasites.

25 October 1944: Temperature rose to 103.4° F. during morning. Second slide positive for malaria (*P. vivax*). Quinine sulfate, 15 gr., three times a day by mouth started.

Four previous smears had been negative for malaria and he had been afebrile for 10 days when the micro-organism was found. White blood counts: 7 October, 12,350 (neutrophils, 80 percent; lymphocytes, 20 percent), 8 October, 5,300 (neutrophils, 74 percent; lymphocytes, 26 percent), 11 October, 11,500 (neutrophils, 64 percent; lymphocytes, 36 percent).

Serology: Kahn, positive, 11 October. Kahn and Wassermann, negative, 17 October. All spinal Kahns negative. Blood bromide, 75 mg. percent, 25 October 1944.

Spinal puncture on 25 October: Pressure 200 mm. of water; 2 white blood cells (lymphocytes); sugar, 56 mg. percent; chlorides, 685 mg. percent. Total protein, 26 mg. percent. Gold curve, 1,111,000,000.

Course: Afebrile on 26 October 1944, and since. Cleared mentally. All neurological signs cleared up except the homonymous field defect which was still present when he was transferred.

Regardless of some diagnostic confusion, all medical officers in the theater acquired a wholehearted respect for the cerebral manifestations of the disease. The grave prognosis of the frank cerebral syndrome and the serious implications of persistent vomiting in *falciparum* infections were quickly learned, and this was responsible for the early institution of vigorous therapy in such cases.

Cachexia

As with cerebral malaria, the incidence varied widely as reported by the various hospitals because of lack of uniformity in the criteria for diagnosis. When the discussion was limited to chronic, truly cachectic states, 12 hospitals reported a total of only 26 cases. It is probable that the theater experience did not greatly exceed this figure. Many medical officers noted that the American soldier stood repeated attacks of *vivax* malaria remarkably well, and a study in the South Pacific confirmed their impression.

From the reports cited, it can be seen that in all theaters of operations in which command and medical officers found malaria a major problem their experiences were very similar, and the stages of their education in dealing with this disease were painfully alike. Rarely has the old adage, "Experience is a hard teacher" been so well illustrated in the annals of medico-military history. The same prejudices, the same mistakes, the same fumblings, and the same slow correction of errors in tactical and medical thinking mark the evolution toward solution of the problem of malaria as exhibited in the reports of the consultants in medicine. Lack of foresight, on the one hand, caught us with scant supplies of quinine; on the other hand, enterprise and ingenuity found ways to improve upon quinine. Under the pressures of war, we learned the chapter on malaria and expanded the section on chemother-

apy. Military medicine, like war itself and the events that lead to war, is full of such ironies; of failures to do something relatively simple that would save much trouble, and then doing something prodigious under the most trying circumstances; in other words, of the human capacity for getting ourselves into the most dreadful difficulties, and then, by summoning great vigor, intelligence, and fortitude, getting ourselves out again. The great wars of our times might be in general so described. The question for the future is how long the human race can take its victories by hairsbreadth; whether, as the wheel spins, we shall always come out on top.

CHAPTER XVIII

Clinical Trials of Antimalarial Drugs

Harry Most, M.D.

Extensive military operations in various highly malarious regions during the Second World War stimulated intensive research in the chemotherapy of malaria. Interruption of the normal supplies of quinine from the Far East made it necessary, while conserving existing supplies, to reevaluate the efficiency of Atabrine (quinacrine hydrochloride) and other agents with known antimalarial properties and to widen the search for new drugs for the treatment, suppression, and possible cure of malaria.

Numerous investigations were carried out by civilian, military, and public health research groups under contract of the Office of Scientific Research and Development, Committee on Medical Research of the National Research Council, and integrated by the Board for the Coordination of Malarial Studies.[1] Approximately 15,000 compounds were studied, and the more promising were given detailed pharmacological and toxicological examination prior to testing in human beings. Important contributions to the knowledge of chemotherapy of malaria resulted from this comprehensive program. Quinacrine proved as good as quinine in most, and superior in some, aspects of treatment. New agents were found that proved superior both to quinacrine and quinine. In addition, other drugs which apparently produce definitive cure of malaria were later found.

The principal purpose of this chapter is to review briefly some of the clinical drug trials made during World War II in relation to their military application in the management of malaria. A note is added on some of these studies as continued, still under the auspices of the U.S. Army, and brought to significant conclusions in the immediate postwar period (p. 594).

PENICILLIN

The occurrence of acute attacks of malaria in military patients who were given large amounts of penicillin for surgical or other infections suggested very early in experience with this antibiotic that it would have no value in the treatment of malaria. Failures to terminate acute attacks with penicillin in amounts of 460,000 to several million units were reported. The im-

[1] A Joint Body Composed of Representatives of the Office of Scientific Research and Development, the Army, the Navy, the U.S. Public Health Service, and the National Research Council, vols. I–VII. [Official record.]

pression was further confirmed in the treatment of neurosyphilis with penicillin and in the treatment of fever induced by malarial infection (transmitted by *Plasmodium vivax* and *Plasmodium malariae*).[2] Of the patients who had remissions of fever, the larger percentage (31 percent of 147 patients) had had no penicillin during therapeutic malaria; the smaller percentage (13 percent of 46 patients) were given 30,000 units every 3 hours for 120 doses, beginning the day after a rise in temperature to 103° F. Again, 15 patients were inoculated with the McCoy strain of *P. vivax* and studied under various schemes of treatment with penicillin. Each patient received 3 million units.[3] This therapy did not reduce the fever, after the cycle of activity, or affect the degree of parasitemia; it did not prevent, postpone, or alter the nature of the attack (chart 26). Penicillin had evidently no place in the prevention, treatment, or suppression of malaria.

HEAVY METALS

Arsenicals.—Arsenated benzine compounds (arsphenamine, neoarsphenamine, and oxophenarsine hydrochloride (Mapharsen)) commonly used in the treatment of syphilis have for a long time been known to possess antimalarial properties in varying degrees. Studies made before and during World War II[4] showed that they were ineffective against infections caused by *P. malariae* and *P. falciparum*. Given intravenously, intramuscularly, or orally, arsenicals were found to possess definite activity in terminating the paroxysms and parasitemia of malaria due to *P. vivax*, particularly in blood-induced infections; in naturally acquired malaria ascribed to *P. vivax*, they proved inferior to quinacrine, quinine, and other drugs as regards control of fever, parasitemia, and the interval to relapse. It was found that their intensive use is not without danger, that they offer no practical advantage over more effective drugs, and finally that arsenicals administered alone or in conjunction with quinacrine or bismuth do not affect the natural relapse rate of this disease.

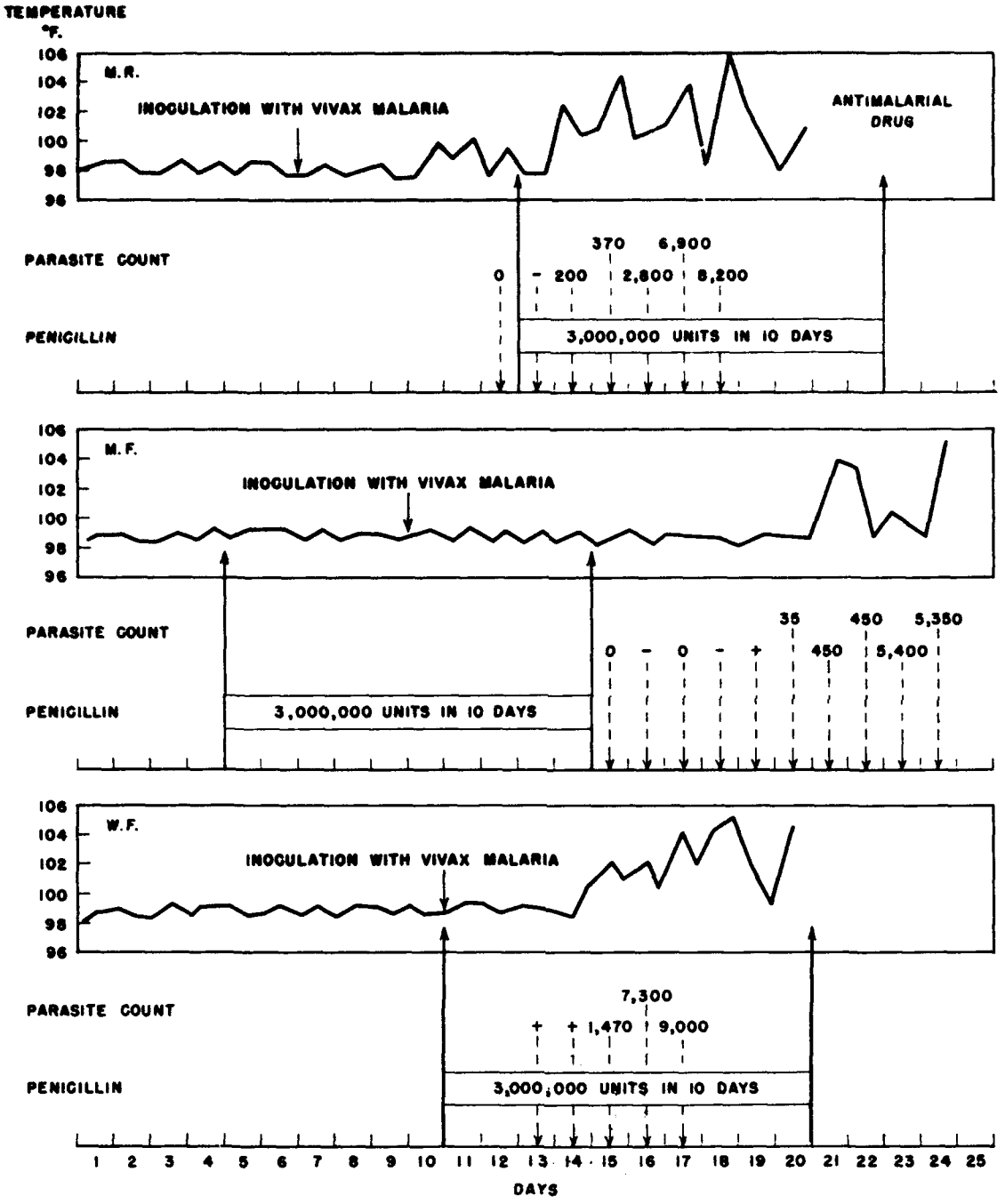
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[2] Personal communication, Maj. Harry H. Gordon, MC, Chief of Communicable Diseases, Harmon General Hospital, Longview, Tex., to the author.

[3] Hindle, J. A., Rose, A. S., Trevett, L. D., and Prout, C.: The Effect of Penicillin on Inoculation Malaria: A Negative Report. New England J. Med. 232: 133–136, 1 Feb. 1945.

[4] (1) Werner, H.: Das Ehrlich-Hata Mittel 606 bei Malaria. Deutsche med. Wchnschr. 36 (Pt. 2): 1792–1794, 29 Sept. 1910. (2) Curd, F. H. S.: The Activity of Drugs in the Malaria of Man, Monkeys, and Birds. Ann. Trop. Med. 37: 115–143, September 1943. (3) Goldman, D.: The Use of Mapharsen in the Treatment of Malaria. Am. J.M. Sc. 196: 502–509, October 1938. (4) Morrison, W. H., and Hill, E. R.: Use of Mapharsen in Relapsing Tertian Malaria. [Official record.] (5) Kay, C. F.: Failure of Mapharsen as an Adjuvant to Atabrine in the Treatment of Relapsing Tertian Malaria. J.A.M.A. 127: 984, 14 Apr. 1945. (6) Spector, S., Haviland, J. W., and Coggleshall, L. T.: The Ineffectiveness of Intensive Mapharsen, Bismuth, and Carbarsone as Curative Drugs for Chronic Malaria. Am. J. Trop. Med. 25: 463–467, November 1945. (7) Bispham, William N.: Malaria: Its Diagnosis, Treatment and Prophylaxis. Baltimore: Williams & Wilkins Co., 1944.

CHART 26.—*Penicillin studies in three patients*[1] *with* vivax *malaria*



[1] Patient M.R. received penicillin after the development of parasitemia and fever. Patient M.F. received penicillin several days before the inoculation of malaria. Patient W.F. received penicillin on or about the same day as the malarial inoculation.

Bismuth compounds.—In one study [5] reported during World War II, it was shown that prolonged courses of bismuth subsalicylate in conjunction with intensive Mapharsen therapy did not reduce the relapse rate in naturally acquired *vivax* malaria of Pacific origin. Bismuth compounds have some limited value in therapeutic management through their ability to establish tertian periodicity [6] in patients with induced *vivax* malaria who have daily or irregular paroxysms, by interrupting, although not terminating, the infection.

Antimony compounds.—These components have been shown to have antimalarial properties [7] both in *vivax* [8] and *falciparum* [9] infections, but practical application was not found for them in the treatment of *vivax* malaria of Pacific origin. They have been provocative in precipitating clinical attacks of *falciparum* or *vivax* malaria in patients under treatment for kala-azar or schistosomiasis. It is of interest, too, that relapses of *vivax* malaria have occurred in nonendemic areas in patients who had previously received one or more intensive courses of trivalent compounds (stibophen (Fuadin) or tartar emetic) for schistosomiasis japonica, or pentavalent compounds (stibamine glucoside (Neostam) and/or ethylstibamine (Neostibosan)) for kala-azar. The prolonged administration of tartar emetic (30 days or more) in therapeutic amounts (1.8 to 2.25 gm.) in many cases is moderately toxic.

SULFONAMIDES

Shortly after the introduction of the sulfonamides in the chemotherapy of infections, they were found to possess antimalarial activity of varying degree. Although data from many studies [10] indicated their limitations, addi-

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[5] See footnote 4 (6), p. 526.

[6] Young, M. D., McLendon, S. B., and Smarr, R. G.: The Selective Action of Thiobismol on Induced Malaria. J.A.M.A. 122: 492–494, 19 June 1943.

[7] Schmidt, Hans, and Peter, F. M.: Advances in the Therapeutics of Antimony. Leipzig: Georg Thieme, 1938, pp. 80–82.

[8] Cole, H. N., DeOreo, G. A., Driver, J. R., Johnson, H. H., and Schwartz, W. F.: Use of Bismuth Injections to Manage Course of Therapeutic Malaria. J.A.M.A. 115: 422–427, 10 Aug. 1940.

[9] (1) De Nunno, R.: Azione del tartaro stibiato sui gametociti del plasmodium vivax e del pl. falciparum. Ricerche sperimentali. Riforma med. 54: 1599–1601, 22 Oct. 1938. (2) De Nunno, R.: La stimolazione antimoniale del s.r.e. come mezzo terapeutico nella malaria estivo-autumnale chinino-plasmochina-atebrin resistente. Nota preventiva. Riforma med. 51: 1087–1093, 20 July 1935.

[10] (1) Niven, J. C.: Sulphanilamide (Prontosil) in the Treatment of Malaria. Bull. Inst. M. Research, Federated Malay States (no. 4), pp. 1–27, 1938. (2) Niven, J. C.: Sulphanilamide in the Treatment of Malaria. Tr. Roy. Soc. Trop. Med. & Hyg. 32: 413–418, November 1938. (3) Yamamato, K.: Sulfanilimide in Malaria. Japanese J. Dermat. & Urol. 46: 78, 20 Oct. 1939. (4) Chopra, R. N., Das Gupta, B. M., Sen, B., and Hayter, R. T. M.: Prontosil in Indian Strains of Malaria. Indian M. Gaz. 74: 321–324, June 1939. (5) De Leon, A. D.: El paludismo y su Tratamiento Intra-venoso por las Sulfanilimidas. Medicina, México 20: 551, 10 Nov. 1940. (6) Chopra, R. N., Hayter, R. T. M., and Sen, B.: M. & B. 693 in Indian Strains of Malaria. Indian M. Gaz. 74: 658–660, November 1939. (7) Coggeshall, L. T., Maier, J., and Best, C. A.: Effectiveness of 2 New Types of Chemotherapeutic Agents in Malaria. J.A.M.A. 117: 1077–1081, 27 Sept. 1941. (8) Johnson, C. E., Jr.: Status of Sulfonamide Therapy in Malaria. Am. J.M. Sc. 206: 327–336, September 1943. (9) Schwartz, L., Furst, W., and Flippin, H. F.: Sulfathiazole as an Antimalarial. Am. J. Hyg. Sect. C 34: 160–162, November 1941.

tional trials were undertaken to determine their suppressive and clinical value in malaria of war origin. Observations showed quite definitely that sulfonamides do not affect the relapse rate of *vivax* malaria, and successful termination of acute attacks was achieved only with large doses, which not infrequently resulted in sulfonamide toxicity. Fever and parasitemia were not controlled promptly, and relapses occurred early following treatment. In short, sulfonamides were inferior to quinine or quinacrine in terminating acute attacks. They were found to be more effective in malaria caused by *P. falciparum.* In a study from West Africa, four out of six sulfonamide compounds exerted a definite effect on fever and parasitemia, but all of them were considered inferior to quinine and quinacrine in the treatment of *falciparum* infections.

It was observed that sufonamides used in the treatment of bacterial infections may suppress parasitemia due to *P. falciparum* or *P. vivax* and so delay the diagnosis of malaria in patients currently or recently under treatment for pneumonia or other infections.[11]

Field studies were conducted in various theaters. It had previously been shown that plasma levels of 4 mg. percent or higher maintained for 28 days after the inoculation of trophozoites of *P. falciparum* prevented the subsequent development of this infection but failed to suppress experimentally induced infections with *P. vivax.* In a series of brilliantly conceived and executed experiments by Australian research teams on the chemotherapeutic, suppressive, and prophylactic activity of various drugs, it was demonstrated that daily doses of 1 gm. of sulfamerazine, sulfadiazine, or sulfamethazine would effectively suppress *falciparum* malaria but would prove ineffective against infections with *P. vivax.*[12]

The practical application of sulfamerazine as a suppressive agent in various field studies is summarized in table 73. These observations show that sulfamerazine in daily doses of 0.5 gm. was not a causal prophylactic, that cyanosis and other manifestations of toxicity were not uncommon, that more clinical attacks occurred during suppression with sulfamerazine than with quinacrine and that they occurred sooner after discontinuance of the drug, and that sulfamerazine exhibited a high degree of suppressive activity but was inferior to 0.6 gm. quinacrine weekly.

Thus, the sulfonamides at most have only limited if any value in the practical treatment or suppression of malaria during war or in civilian life if quinine, quinacrine, or equally effective agents are available.

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11 Page, S. G., Jr., and McCall, J. V., Jr.: Delay in Diagnosing Malaria After Sulfadiazine Therapy; Two Case Reports. South. M.J. 39: 728–731, September 1946.

12 Fairley, N. H.: Chemotherapeutic Suppression and Prophylaxis in Malaria; An Experimental Investigation Undertaken by Medical Research Teams in Australia. Tr. Roy. Soc. Trop. Med. & Hyg. 38: 311–365, May 1945.

TABLE 73.—*Experimental field tests with sulfamerazine, Atabrine, and sulfapyrazine*

Drug	Dosage	Days of exposure	Days of drug	Number of subjects	Number of breakthroughs	Number of infections	Total malaria cases	Duration of followup
				Panama [1]				
Sulfamerazine	0.5 gm. daily	32	42	111	2 *vivax*	4 (3 *vivax*, 1 *falciparum*)	6 (5 *vivax*, 1 *falciparum*)	30 days.
Atabrine	0.4 gm. weekly	32	42	109	0	2 (1 *vivax*, 1 *falciparum*)	2 (1 *vivax*, 1 *falciparum*)	
				Southwest Pacific Area [2]				
Sulfamerazine	0.5 gm. daily	44	54	99	1 *falciparum*	34 (28 *vivax*, 3 *falciparum*, 3 mixed)	36 (29 *vivax*, 4 *falciparum*, 3 mixed)	57 days.
Do	1.0 gm. daily	44	54	12	1 *vivax*			
Atabrine	0.6 gm. weekly	44	54	107	0	25 *vivax*	25 *vivax*	
				Southwest Pacific Area [3]				
Sulfamerazine	0.5 gm. daily	33	30+17 on Atabrine.	100	2	6	8 (5 *vivax*, 2 *falciparum*, 1 mixed)	30 days.
Atabrine	0.4 gm. weekly	33	42	114	10	23	31 (15 *vivax*, 9 *falciparum*, 7 mixed)	
				India [4]				
Sulfamerazine	0.5 gm. daily	31	39	200	14		14	4 days.
Atabrine	0.4 gm. weekly	31	39	200	9		9	Do.
				West Africa [5]				
Sulfapyrazine	0.5 gm. daily	------	--------	140			4	----------
Atabrine	0.4 gm. weekly	------	--------	140			24	----------

[1] In the control group for the experimental field tests conducted by Col. Wesley C. Cox, MC, in Panama, 281 subjects were kept under rigid malaria control and discipline. There were four cases of malaria and all suffered breakthroughs caused by *vivax* infections. None suffered infections following suppressive treatment. Duration of followup after therapy was 30 days.

[2] In the field tests conducted by Col. Maurice C. Pincoffs, MC, in the Southwest Pacific Area, there were 51 subjects who had been exposed to malaria for 44 days and had received a malaria suppressive for 54 days. There were 32 cases of malaria of which 17 suffered breakthroughs. There were eight breakthroughs due to *vivax* infections, eight to *falciparum* infections, and one mixed infection. Eight suffered infections after suppressive treatment, five were *vivax* infections, two *alciparum* infections, and one mixed infection.

[3] Tests conducted by Col. Earl Maxwell, MC.

[4] Tests conducted by R. N. Chopra.

[5] Tests conducted by Brigadier G. M. Findlay.



U.S. Army photograph

FIGURE 60. Brig. Gen. James S. Simmons and Col. Arthur Fischer, GSC, inspect cinchona seedlings, November 1943. These are being grown in a cinchona seedling hothouse near Washington, D.C., for shipment to South America to be used in production of quinine for treatment of malaria.

CINCHONA ALKALOIDS

Quinine

With the loss, early in the war, of the main sources of quinine, for centuries the drug of choice in the treatment of malaria, the problem of supply was considered sufficiently critical to warrant restriction of cinchona alkaloids to essential purposes in two War Production Board orders.[13] If quinine was to be allocated almost exclusively to the Armed Forces, some substitute would have to be made available for civilian use (fig. 60). It was desirable also to find out exactly how efficient the cinchona alkaloids were in the treatment or suppression of malaria, and whether they would be significantly practical for military use. Discussion in this section will be limited to a few important observations in respect to the relative efficiency of quinine or other cinchona alkaloids in the treatment and suppression of malaria.

[13] War Production Board, Conservation Orders No. 131, 30 Apr. 1942 and No. M 131 a, 19 June 1942.

Acute attacks

It had been shown that plasma concentrations of quinine of 4.5 mg. per liter (dosage range 0.12 to 1.8 gm. daily) were effective in suppressing and in terminating acute attacks of *vivax* malaria. Plasma levels of 5.5 mg. per liter suppressed and terminated acute attacks of *falciparum* malaria.[14] Nevertheless, in a field-type experiment with New Guinea strains, daily doses of 0.6 gm. failed to prevent attacks of *falciparum* malaria, and 0.3 gm. daily was incapable of preventing *vivax* attacks. When the latter dose was increased to 0.6 gm., complete suppression was achieved in some cases of infection with *P. vivax* but not in others. By contrast, daily doses of 0.1 gm. of quinacrine were completely effective in suppressing infections with either agent.

In West Africa, daily suppressive doses of 0.3 gm. quinine were associated with a malaria rate of 651 per 1,000 in a group of 1.180 men, with 4 cases of blackwater fever. In another group of 96 men given 0.3 gm. of quinine daily, 70 developed clinical malaria while on this regimen and 7 more while being transferred to quinacrine. On the other hand, in 752 men on relatively small doses of quinacrine (0.4 gm. weekly), the rate was 450 per 1,000 with only 1 case of blackwater fever. This definite discrepancy in attack rate would doubtless have been larger if they had been given what was subsequently found to be the optimum dosage of quinacrine (0.7 gm. weekly).

Relapses

Clinical studies in this country were undertaken[15] to determine the effectiveness of maximum doses of quinine in terminating acute attacks of relapsing *vivax* malaria of Pacific origin. The following results were reported in a comparative study of a group of 100 patients treated with 28.35 gm. of quinine during 14 days and a control group of 150 patients treated with 2.8 gm. of quinacrine during 7 days: The mean level of quinine in the plasma during treatment was 7.3 mg. per liter, well above the demonstrated effective range. Both groups had blood-smear examinations twice weekly after completion of treatment and were observed for 120 days for clinical or parasitemic relapse.

Special considerations

Control of parasitemia.—As shown in chart 27, quinacrine proved significantly superior to quinine in rapidly clearing the blood of malarial parasites, in some patients within 12 hours of the first dose. At 24 hours, 26

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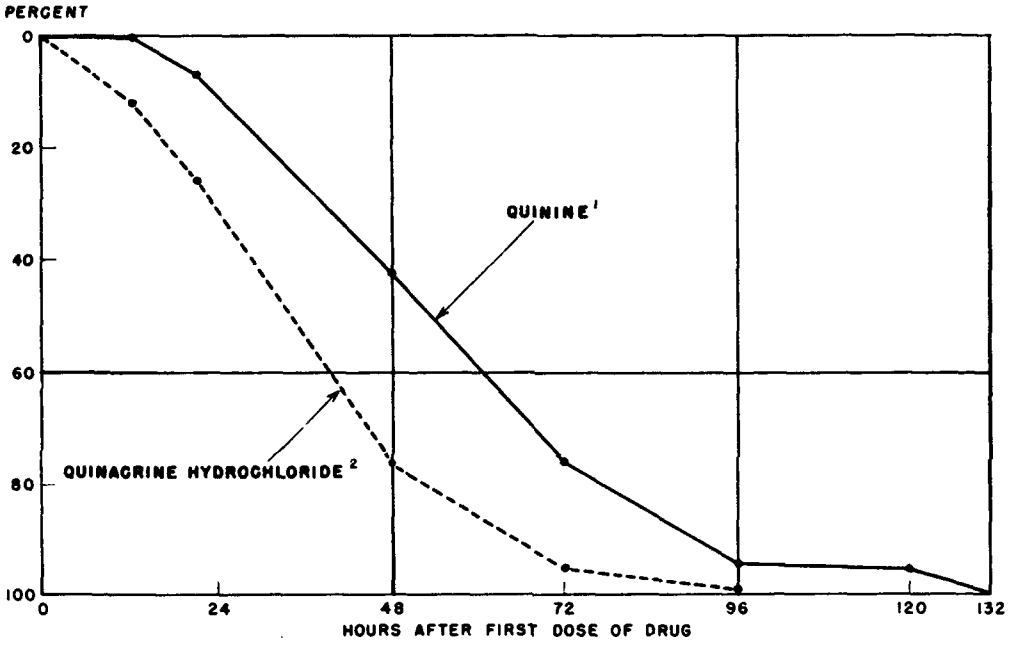
[14] Bi-Monthly Progress Report No. 12, Committee on Medical Research, Office of Scientific Research and Development, 1 Sept. 1943, subject: Malarial Chemotherapy, Contract No. OEMcmr-112.

[15] (1) Most, H., and Hayman, J. M., Jr.: Relative Efficiency of Quinacrine (Atabrine) and Quinine in Treatment of Acute Attacks of Vivax Malaria. Am. J.M. Sc. 211: 320-324, March 1946. (2) Gordon, H. H., Christianson, H. B., and Lippincott, S. W.: A Comparison of Quinine and Quinacrine in the Treatment of the Clinical Attacks of Vivax Malaria. South. M.J. 39: 631-634, August 1946.

percent of those treated with quinacrine and only 7 percent of those given quinine were free of parasites, as were 77 percent and 44 percent, respectively, at 48 hours. At 72 hours, only 4 percent of patients treated with quinacrine still showed parasites, and all were clear at 96 hours; almost one-fourth of the patients treated with quinine still had parasitemia at 72 hours, and in a few this persisted as long as 132 hours.

CHART 27.—*Rate of disappearance of parasites during treatment of 497 acute attacks of* vivax *malaria with quinacrine hydrochloride or quinine*

[Rate expressed as percentage of patients with negative smears]



[1] Total dose: 28.35 gm.; duration: 14 days (100 patients).
[2] Total dose: 2.8 gm.; duration: 7 days (397 patients).

Control of fever.—The idea frequently advanced that quinine should be used during the first few days of an acute attack because of its superiority in controlling fever quickly was not borne out in this study. Quinine was not significantly more effective in this respect in relapses and was in fact less effective in patients with delayed primary attacks, of whom 32 percent had fever on the second or third day after beginning treatment with quinine, as compared to 16 percent with quinacrine.

Control of other symptoms.—It is difficult to evaluate, in relation to therapy, data on such symptoms as headache, backache, nausea, malaise, and weakness, which usually occur in an attack of malaria. Statistically, there was little difference in the duration of these symptoms under treatment with one or the other drug, although clinically one had the impression that such symptoms, particularly weakness and anorexia, were more promptly controlled with quinacrine.

Toxicity.—Persistent vomiting associated with the malarial attack was controlled by withholding fluids and food by mouth and by giving intravenous glucose prior to the administration of quinacrine. Given several hours of freedom from vomiting, this symptom was not brought on again by the drug.

Gastrointestinal disturbances controlled as described were not aggravated by quinine. Patients with eczematoid or exfoliative dermatitis and malaria had no activation of the skin process attributable to quinine. One patient, who proved to be hypersensitive to the dru[illegible] acute thrombopenic purpura and severe angioneurotic edema of [illegible]he first day of treatment. Such reactions, although not unknown, were admittedly rare. A fairly high proportion of patients treated with quinine, however, complained of severe and annoying tinnitus and fullness in the ears or head. In many cases, this seemed to retard full recovery from the symptoms of an acute attack.

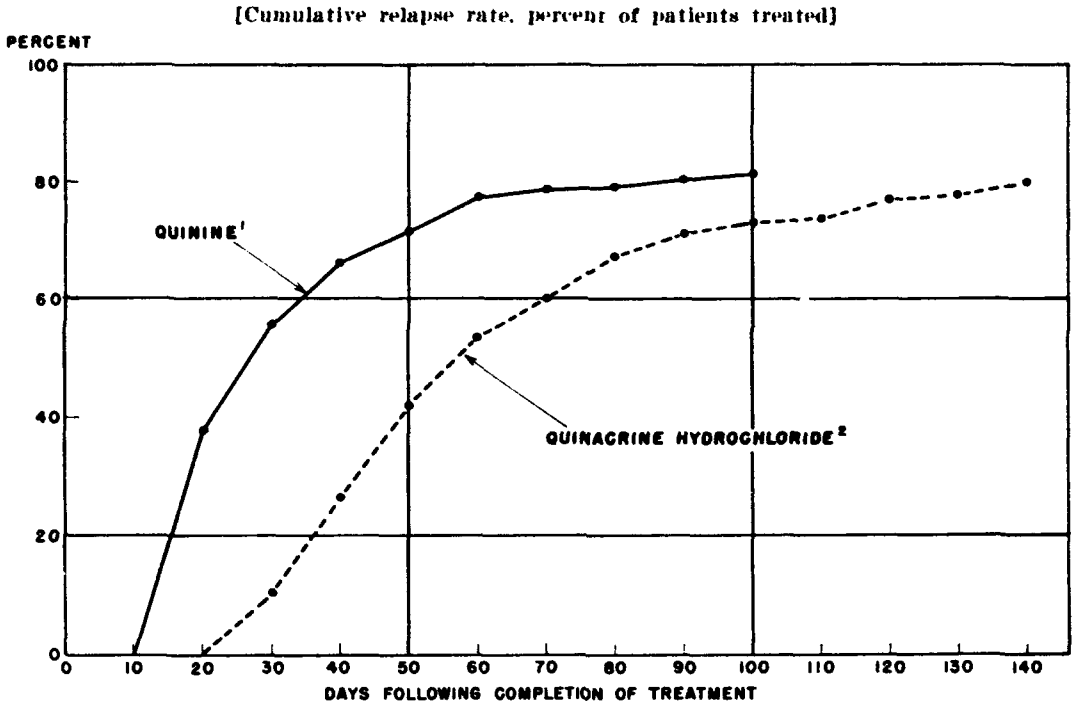
No major toxic manifestations were seen during treatment with quinacrine. Patients who alleged previous intolerance to the drug displayed none when it was given to them in colored capsules without their knowledge of the contents. In this series, signs and symptoms referable to the central nervous system were not encountered in relation to quinacrine therapy. Two patients with severe eczematoid dermatitis and acute malaria who were not having specific antimalarial treatment had flareups of the skin process, and many others with the two conditions suffered no ill effects from treatment with quinacrine.

Relapse rate and interval to relapse.—Approximately 80 percent of Pacific infections relapsed within the observation period of 120 days, whether treated with quinacrine or quinine, but there was a striking difference in the length of the interval to relapse. In short, the mean interval following treatment with quinine was 22 days as compared with 53 days following treatment with quinacrine (chart 28). Quinacrine thus effected a longer interval to relapse by at least a month, reducing to a minimum the number of relapses occurring within 30 days of treatment and in 30 percent of cases prolonging the interval to more than 60 days.

Falciparum *infections*

Single intravenous injections of as much as 1.2 gm. of quinine failed to terminate acute attacks caused by *P. falciparum* in 5 out of 10 patients, while intravenous injection of single doses of 0.4 to 1.0 gm. of quinacrine terminated attacks due to *P. falciparum* in 49 out of 50 cases at the 20th General Hospital, India-Burma theater. The relative merits of parenteral quinine and quinacrine in fulminating *falciparum* infections are discussed in the section on quinacrine. Maximum doses of quinine have been shown to produce more minor and major toxic manifestations than therapeutic amounts of quinacrine. Aside from cinchonism, quinine used in 10,000 cases of ma-

CHART 28.—*Relapse rates and intervals to relapse following treatment, by days, with quinacrine hydrochloride or quinine of 250 acute attacks of* vivax *malaria of Pacific origin*



[1] Total dose: 28.35 gm.: duration: 14 days (100 patients).
[2] Total dose: 2.8 gm.; duration: 7 days (150 patients).

laria was associated with an incidence of purpura in 5 percent, with 2 deaths, whereas no case of purpura occurred in 2,500 cases treated with quinacrine in Panama.[16] Fatal bullous erythema following 1.95 gm. and severe dermatitis after 15 gm. of oral quinine were reported in two patients in India. In addition, gluteal abscesses from intramuscular quinine and convulsions followed by death during or shortly after intravenous quinine occurred in eight patients.[17]

Summary of comparative studies

There remained little question, therefore, after consideration of the data presented, that quinine is a relatively inferior drug in the treatment of acute attacks of *vivax* malaria or in the suppression of infections with *P. vivax* or *P. falciparum* in nonimmune military personnel. Its early use in the Pacific combat areas resulted in numerous "breakthroughs" of *falciparum* and *vivax* malaria during suppression and in early and repeated relapses of the latter. Fortunately, quinacrine was available in adequate amounts, and its establishment as the standard drug resulted in effective suppression and satisfactory control of clinical attacks.

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[16] Shrager, J., and Kean, B. H.: Purpura as a Complication of Malaria. Am. J.M. Sc. 212: 54–59, July 1946.
[17] Essential Technical Medical Data, India-Burma Theater, for June 1945.

Totaquine

Totaquine (containing not less than 7 percent nor more than 12 percent of anhydrous quinine and not less than 70 percent nor more than 80 percent of total anhydrous crystallizable cinchona alkaloids) was studied at several general hospitals in the Zone of Interior and overseas. Relatively large amounts were available and more could be obtained for civilian or military use. The antimalarial qualities of all the cinchona alkaloids it contained, if additive, could result in substantial saving in quinine and other alkaloids.

In a study carried out at Kennedy General Hospital, Memphis, Tenn., in July 1944, totaquine proved as effective as quinine in terminating acute attacks of malaria due to *P. vivax* of Pacific origin, but it more frequently produced epigastric distress, blurred vision, dizziness, and severe vomiting. Similar findings were reported in a study at Bushnell General Hospital, Brigham City, Utah. In addition to the patients treated for 5 days, 53 were maintained on suppressive doses (0.6 gm. daily) for 55 days. Of these, 13 (about 25 percent) "broke through" with clinical malaria. Of the treated patients, 60 percent relapsed; the average interval to relapse was 34 days after suppressive treatment with totaquine.

At the 31st Station Hospital in New Caledonia, a study of patients in groups of 80 treated with totaquine, quinine, or quinacrine, for relapsing malaria of Pacific origin, again showed not much difference as to control of parasitemia, fever, and other symptoms.[18] Again nausea, vomiting, vertigo, and blurred vision were observed with totaquine and in some cases were severe. Relapses began within 1 week after completion of treatment with totaquine or quinine, reaching their peak in 2 weeks, whereas relapses after quinacrine did not begin until 3 weeks after completion of treatment and reached their peak at 6 weeks. Similar findings were reported from two Army hospitals in another theater.

In summary, these studies indicate that totaquine is as efficient as quinine in terminating acute attacks of malaria, but is more toxic. Moreover, like quinine, totaquine is less effective than quinacrine in controlling fever and parasitemia and in shortening the intervals between relapses.

These factors, in addition to its being inefficient as a suppressive, variable in alkaloid content, and difficult to standardize, would preclude the use of totaquine on a wide scale for military purposes. It could, however, have a useful role in the treatment of malaria in highly immune individuals in whom small amounts of any antimalarial agent are effective in terminating periods of clinical activity. A considerable advantage in the use of totaquine in areas where it is locally available would be the relatively low cost and ease of preparation, permitting the use of low grade barks of poor quinine content.

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[18] Green, R. A.: Totaquine in the Treatment of Malaria. Bull. U.S. Army M. Dept. No. 84, pp. 51-57, January 1945.

Other Cinchona Alkaloids

Dihydroquinine, more commonly known as hydroquinine, offered an interesting possibility because it not only could be totally synthesized but could be obtained in 95 to 100 percent yield from the hydrogenation of quinine. If the higher therapeutic activity of dihydroquinine claimed for it in studies of malaria in birds could be demonstrated in man, a useful substitute for quinine might be available synthetically, or the effective stores of quinine could be increased from 15 to 20 percent by converting the latter to dihydroquinine. However, clinical tests in the Pacific with total daily doses of 0.3 to 1.8 gm. for 6 days in relapsing *vivax* malaria failed to show any greater therapeutic activity of dihydroquinine over quinine. One patient complained of blurred vision after a total of 0.6 gm., and three other men receiving 0.3 gm. three times daily complained of vertigo (two patients) and weakness in the legs (one patient). Dihydroquinine therefore offered no advantage over quinine.

The antimalarial activity of quinidine, cinchonine, and cinchonidine have been known for a long time, and their ability in terminating clinical attacks of malaria was demonstrated many years ago.[19] Quinidine as an antimalarial was not explored extensively because of its potential cardiac toxicity, nor were cinchonine and cinchonidine, individually representing small fractions of the total cinchona alkaloids. Development of chemical methods[20] for estimating plasma levels of these alkaloids made it possible to evaluate their relative antimalarial activity in man. It was shown that plasma levels of 0.1 and 0.5 mg. per liter for cinchonine and 2.5 and 3.0 mg. per liter for cinchonidine for clinical control of acute attacks of malaria were effective against *vivax* and *falciparum* infections, respectively, and that these levels were attained with daily doses of 2.0 to 3.0 gm. of cinchonine and 1.0 to 3.0 gm. of cinchonidine. The effective levels of quinine are 4.0 mg. for *vivax* infections and 5.0 mg. for *falciparum* infections, although some of the latter may not be controlled with levels as high as 10 mg. per liter. Total daily amounts of 1.5 gm. of quinine (0.65 every 8 hours) will provide levels of 7.0 to 12.9 mg. per liter (average 10.3), which are adequate to control most infections. Although it may appear that cinchonine and cinchonidine are more effective than quinine by virtue of activity at lower plasma levels, it must be recognized that such levels are obtained only with two to four times the amounts of these drugs in comparison with quinine. Consequently, no practical advantage could be derived from the individual use of cinchonine or cinchonidine in the routine termination of attacks of malaria since they would ultimately have to be derived from cinchona itself. No clinical studies with cinchonine or cinchonidine were undertaken in the Army. However, it was concluded

[19] Nelson, E. E.: Cinchona and Its Alkaloids in the Treatment of Malaria. A Symposium on Human Malaria. (Pub. No. 15.) Washington: American Association for the Advancement of Science, 1941, pp. 255–260.

[20] Bi-Monthly Progress Report No. 11, Committee on Medical Research, Office of Scientific Research and Development, 2 July 1943, subject: Malarial Chemotherapy, Contract No. OEMcmr-112.

from civilian studies that they were less toxic than quinine, particularly with respect to symptoms attributable to the special senses, and that these drugs singly or in combination, as in totaquine, should be approximately equivalent to quinine in antimalarial activity.

Summary of Studies

Studies with cinchona alkaloids during the war were therefore of definite practical value. It was demonstrated that totaquine and its component alkaloids were as effective as quinine but more toxic, that the cinchona alkaloids were inferior to quinacrine in both suppression and termination of acute attacks of malaria, and that the loss of quinine was accordingly not a serious military problem. A rational method of assay of antimalarial properties of drugs was developed and the efficiency of the various cinchona alkaloids reevaluated. No conclusive studies on the relative efficiency of parenteral quinine and quinacrine in the treatment of cerebral malaria were reported, and this problem still requires investigation before a final estimate can be made of the role quinine should play in the therapy of malaria.

QUINACRINE HYDROCHLORIDE (ATABRINE) [21]

The extensive prewar literature dealing with the antimalarial properties and toxicity of quinacrine has been adequately reviewed.[22] Following the introduction of this drug in 1931, it became apparent that the originally advocated dosage schedule of 0.1 gm. three times daily for 5 days was in many cases, particularly in severe *falciparum* infections, inadequate for prompt and effective control of fever, symptoms, and parasitemia. There were numerous revisions in treatment plans, but there was no rational pharmacological basis for defining what dosage and treatment schedules were best for terminating acute attacks or for suppression. The relative efficiency of quinacrine versus quinine had not been established, and it was questionable whether we would be able to produce adequate amounts of effective antimalarial drugs. Numerous studies were conducted in many laboratories and hospitals in the various theaters. It is the purpose of this section to review briefly basic clinical and other observations that established quinacrine as a highly effective and satisfactory antimalarial during the war.

In 1941, American chemists succeeded in completely synthesizing quinacrine. Chemical, pharmacological, and clinical investigations sponsored by the National Research Council established the identity of the German and American drugs and found no appreciable difference between them as regards side reactions. Rumors that the American preparation was not identical with the German drug could be definitely dismissed. Finally, tremendously increased production assured an adequate supply at least for military use at first and later for civilian and lend-lease purposes.

[21] Formula: 3-Chloro-7-methoxy-9-(1-methyl-4-diethylamino-butylamino) acridine dihydrochloride.

[22] See *footnote* 4 (7), p. 526.

General Properties

Practical, highly sensitive, and accurate chemical methods for the estimation of quinacrine concentrations in the blood and tissues made it possible to study its physiological disposition in the human body.[23] It was shown that:

> * * * Atabrine is almost completely absorbed in the gastrointestinal tract and renal excretion accounts for very little of the daily dose. It may be concluded from these facts and the fact that its plasma concentration becomes stabilized after several days of drug administration at constant dosage, that it is disposed of by the body mainly by processes which result in its degradation. It follows, then, that the major factors which will relate drug administration and plasma drug concentration are those which condition the processes of distribution and degradation in the body.
>
> * * * It was found that the concentration of the drug in plasma, erythrocytes, and leukocytes is in the order of 1, to 1, to 100–200.
>
> * * * Studies * * * in experimental animals indicated that the drug may achieve concentrations in the liver and spleen as high as 10,000–20,000 times those currently observed in the plasma. Localization in other tissues was found to be less extensive, but highly significant. An extension of these distribution studies to the human [subject] * * * demonstrated that a major portion of the administered Atabrine is localized in the tissues of the body, leaving little in the plasma to exert a chemotherapeutic effect. It is in consequence of this that unless large initial doses of the drug are given the initial plasma drug concentrations are invariably low. However, the extensive localization, together with the low rates of degradation and renal excretion, lead to a low rate of decline of the plasma Atabrine concentration, and consequently a low rate of loss of the protection conferred by Atabrine, subsequent to the termination of drug administration.

It was apparent that a rational regimen of quinacrine therapy would have to be designed along the commonly accepted principles of chemotherapy; namely, the administration of sufficient drug when the diagnosis of malaria is made, or when exposure to malaria is anticipated, to obtain the desired plasma concentration, followed by the serial administration of small doses to maintain it.

The next step was to determine the plasma levels of quinacrine that would be effective in the prompt control of symptoms, fever, and parasitemia associated with acute attacks of *vivax* and *falciparum* infections. Infections with various strains of *P. vivax* and *P. falciparum*, transmitted by mosquitoes or introduced by blood, were established in volunteers and paretics, and different amounts of quinacrine in different treatment schedules were used to produce various plasma concentrations. It was found that if quinacrine concentrations of 30 μg. per liter or more were maintained for 4 days in *vivax* infections there was complete termination of clinical activity and parasitemia. Levels between 10 and 30 μg. per liter produced temporary or partial effects,

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[23] (1) Brodie, B. B., and Udenfriend, S.: The Estimation of Atabrine in Biological Fluids and Tissues. J. Biol. Chem. 151: 299–317, November 1943. (2) Mackie, Thomas T., Hunter, George W., III, and Worth, C. Brooke: Manual of Tropical Medicine. Philadelphia: W. B. Saunders Co., 1945, pp. 675–677. (3) Shannon, J. A., Earle, D. P., Jr., Brodie, B. B., Taggart, J. V., and Berliner, R. W.: The Pharmacological Basis for the Rational Use of Atabrine in the Treatment of Malaria. J. Pharmacol. & Exper. Therap. 81: 307–330, August 1944.

and levels below 10 μg. per liter produced little or no effect when maintained for 4 days. Infections with *P. falciparum* required approximately 50 μg. per liter maintained for 6 days for termination of clinical activity and parasitemia.

With the treatment schedule for quinacrine commonly used before 1943 (0.1 gm. three times daily for 5 days), very low concentrations in the plasma were achieved during the first 2 or 3 days of therapy because of the extensive localization of the drug in tissues. If such dosage is continued for a period of days, the plasma levels will rise progressively, as more and more drug accumulates in the tissues, until ultimately they reach sufficient height to terminate the attack. The delay in the initial effect of quinacrine in such a dosage schedule had led to the belief that quinacrine therapy should be preceded by a 2- to 3-day course of quinine. Actually, such a course is undesirable because 24 hours or less after the last dose the plasma level of quinine is no longer effective. If parasitemia is still present, as it often is in cases so treated, there will be a reactivation of the disease during the next few days (of treatment with 0.1 gm. quinacrine three times a day) until the plasma quinacrine level in this schedule becomes effective.

If, on the other hand, total doses of 0.8 to 1.0 gm. of quinacrine are given orally during the first 24 hours of therapy, or by a combination of parenteral and oral routes, high effective plasma concentrations are quickly established and easily maintained by the serial administration of 0.1 gm. three times daily for 6 days. These considerations led to the adoption by the U.S. Army of a standard course of quinacrine therapy consisting of 2.8 gm. during 7 days (1.0 gm. the first 24 hours and 0.3 g.m. daily for 6 more days).[24]

Clinical Use

In acute attacks.—Clinical experience in this country and overseas proved conclusively the efficiency of such a regimen in terminating acute attacks of malaria due to *P. vivax* and *P. falciparum*. It was found[25] that 2.8 gm. of quinacrine administered as recommended in Circular Letter No. 153, Office of the Surgeon General, 19 August 1943, brought about cessation of fever within 24 hours in approximately 90 percent of cases of *vivax* malaria and in the remainder within 48 to 72 hours; approximately 80 percent of patients had negative smears within 48 hours and almost 100 percent at 96 hours. Relapses after treatment with quinacrine occurred in an average of 53 days, in contrast to 24 days and the many short-term relapses following treatment with quinine. In the treatment of acute attacks, there were no toxic manifestations similar to those induced by prolonged intensive treatment with quinine.

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[24] Circular Letter No. 153, Office of the Surgeon General, U.S. Army, 19 Aug. 1943, subject: The Drug Treatment of Malaria, Suppressive and Clinical.

[25] See footnote 15, p. 532.

In 291 patients, plasma levels were determined during and after 412 attacks of *vivax* malaria acquired in the South Pacific.[26] The average daily levels from the second to the eighth days of treatment with quinacrine were 41 to 52 μg. per liter. The average increase in level 2 to 4 hours after a dose of 0.1 gm. on the second to seventh day was 6.8 to 11.3 μg. per liter above the corresponding fasting level. The average level 4 weeks after completion of 2.8 gm. of quinacrine therapy was 8 μg. per liter. It was found that this regimen produced plasma levels of 45 μg. per liter within 24 hours after treatment was begun and that all symptoms and parasitemia were abolished within 72 hours in almost 100 percent of the patients. No correlation was observed between plasma levels and the occurrence or spacing of relapses.

The question arose whether plasma levels would be affected by such factors as jungle climate, fatigue, combat, and diarrhea. It was shown overseas that diarrhea or dysentery did not influence the pattern of the quinacrine plasma levels during therapy. In this country under simulated jungle conditions, and also overseas, it was shown that high temperatures, humidity, and fatigue did not adversely affect the absorption or stabilization of quinacrine in the plasma.

Quinacrine was found to be effective also in the treatment of delayed primary *vivax* malaria appearing after discontinuance of quinacrine suppression.[27] The continued use of this drug does not produce strains of parasites that are resistant to its action. It was noted that fever and sometimes parasitemia were not so promptly controlled in primary attacks as in relapses, although quinacrine was superior to quinine in both types of attack, and the rate of disappearance of parasites from the blood in a relapse was dependent on the degree of initial parasitemia rather than on the plasma level of quinacrine. This observation has no practical importance, however, since most patients are free of fever and symptoms before parasites have disappeared completely from the blood, and regardless of initial parasite density almost all patients have negative smears within 96 hours after the initiation of an adequate schedule of quinacrine therapy.

Attempts to enhance the response to treatment by increasing the initial or the total dose were made in several oversea installations. However, 2.8 gm. in 3 days, or 3.5 to 4.8 gm. in a week, proved no more effective in controlling the acute attack or affecting subsequent relapse rates than the standard schedule of 2.8 gm. in 7 days. In the control of relapses, short courses of treatment (1.2 gm. in 16 hours or 1.4 gm. in 12 to 16 hours) were effective in terminating acute attacks but, if not followed immediately by suppressive doses, might be succeeded by early relapse or in a malarious area by new infection because of the rapid fall of concentration in the plasma below protective levels. One-

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[26] Ellerbrook, L. D., Lippincott, S. W., Cateno, C. F., Gordon, H. H., and Marble, A.: Plasma Quinacrine Concentration in Treatment of Plasmodium Vivax Malaria Acquired in the South Pacific. Arch. Int. Med. 76: 352–357. November-December 1945.

[27] London, I. M., Kane, C. A., Schroeder, E. F., and Most, H.: The Delayed Primary Attack of Vivax Malaria. New England J. Med. 235: 406-410, 19 Sept. 1946.

day treatment courses or less have only a slight advantage in insuring the administration of adequate amounts of drug in a short time, and little is gained in reduction of nursing care since patients with acute malaria are usually sick for several days. Moreover, unrecognized or severe *falciparum* infections may not be controlled with this amount of medication. A false sense of security may cause carelessness in observation of patients.

A short course totaling 2.2 gm. in 3 days (1.0 gm. on the first day, then 0.6 gm. daily for 2 days) was found, in this country, as effective as 2.8 gm. in 7 days in terminating acute attacks of *vivax* malaria, with a similar spacing of the intervals to relapse. Many patients were symptom free in 3 days, and in some cases the period of hospitalization could be reduced. Relapse of previously treated *falciparum* infections, rarely seen in this country, would not constitute a hazard in 3-day treatment of *vivax* relapses here. Total doses in excess of 2.8 gm. or in periods of less than 7 days are not advocated except possibly in fulminating *falciparum* infections, since nothing is gained by excessive dosage and there is more risk of toxic reactions.

In *falciparum* infections.—The clinical studies discussed thus far have been concerned principally with *vivax* infections. It has been noted that experimentally induced *falciparum* infections were effectively controlled with quinacrine plasma levels in the range of 40 to 50 μg. per liter. Plasma levels in that order are quite uniformly attained by initial doses of 1.0 gm. of quinacrine administered during the first day of treatment by the oral or combined oral and parenteral routes. It was to be expected, then, that standard quinacrine treatment would prove effective in the control of the majority of infections with *P. falciparum*.

In a report from India [28] summarizing the treatment of over 5,000 cases of malaria of which more than two-thirds were due to *P. falciparum*, it was stated that quinacrine was as effective as quinine in terminating them. This is of particular significance since early in that theater's experience the dosage of quinacrine was 0.1 gm. three times a day for 5 to 7 days. Undoubtedly, higher doses on the first day would have produced even more satisfactory results. In fact, 50 patients so treated responded promptly and were afebrile by the third day.

By contrast, patients treated with quinine for the first 2 days had a reactivation of fever on the third day when quinine was discontinued. It was stated that in this study the patients treated with quinacrine remained febrile a little longer than those treated initially with quinine, but the former had considerably less nausea and vomiting and no tinnitus or deafness. Treatment with quinine was associated with the development of blackwater fever in two patients. One patient developed a fatal diffuse bullous erythema after 1.95 gm. of quinine and another developed an extensive dermatitis after 15 gm.

Extensive experience in West Africa and in various Pacific islands where the majority of initial attacks of malaria were due to *P. falciparum* demonstrated the efficiency of standard quinacrine therapy in terminating uncomplicated attacks. In general, its value in the more severe forms of malaria is attested by the remarkably low death rate from this disease during the war in conjunction with the widespread use of quinacrine. Fulminating cerebral malaria was fortunately not common in most theaters.

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[28] Ware, R. E., Brem, T. R., and Crane, N. F.: Experiences With Malaria in India. [Official record.]

In India, of over 6,000 cases of malaria in native or foreign troops there were 140 cases of the cerebral form, or an incidence of about 2 percent of *falciparum* infections.[29] The death rate in American troops with cerebral malaria was 5 percent and in Chinese and other personnel, 33 percent. Quinacrine alone was said to have cured several cases. In another report,[30] it was stated that 1 death occurred in 8 patients with cerebral malaria treated with quinacrine intramuscularly, and 31 deaths occurred in 61 patients treated with quinine parenterally. In the latter group, eight patients had convulsions and died shortly after intravenous injection of quinine. Of five additional patients treated with a single infusion of quinacrine (0.8 to 1.0 gm.) for cerebral malaria, one died; this patient had also received more than 1.0 gm. of quinine intravenously.[31] In the four patients who recovered, parasitemia was controlled within 48 hours. The serum quinacrine levels 24 hours after the infusion was given varied from 100 to 320 μg. per liter. The mortality for cerebral malaria in a series of 146 patients in the Southwest Pacific treated with quinine parenterally was 37 percent and was 21 percent for 19 patients treated with quinacrine.

Parenteral quinacrine treatment thus gave definite evidence of effectiveness in some cases of cerebral malaria. No comparative studies in sufficient numbers were reported on which to base definite conclusions with regard to the relative efficiency of quinacrine and quinine in severe cases with cerebral involvement. The surgeon in the India-Burma theater stated:

> My conclusions as to the relative merits of parenteral quinine and Atabrine (in cerebral malaria) are that I am not certain that either possesses a distinct advantage over the other. Atabrine may have a slight advantage in that (1) it is probably less toxic, (2) its effect persists longer, and (3) it can be given intramuscularly. All data we possess indicate that when given in adequate amounts, it is at least as effective as quinine, and may be more effective. Moreover, if a rapid and prolonged effect is desired 0.8 gm. in a slow intravenous drip (over 4 hours) clears the blood of parasites as rapidly as any other method and a parasiticidal concentration remains in the blood for at least 5 days.[32]

Intramuscular injections of quinacrine were found useful in *vivax* and *falciparum* infections with severe vomiting as a means of attaining high plasma levels promptly. For example, single doses of 0.4 gm. given intramuscularly result in levels of 168, 327, 297, 155, 89, 60, 45, 37, and 20 μg. per liter at 5, 15, 30, 60 minutes and 2, 3, 5, 8, and 24 hours, respectively, after injection. Serial injections of 0.2 gm. at intervals of 4 to 8 hours for 24 hours or more can be expected to maintain high effective levels until oral medication can be instituted.

Following a single intramuscular dose of 0.2 gm. of quinacrine, it was shown[33] that the number of motile parasites with finely dispersed pigment was reduced and the number of nonmotile parasites with clumped pigment was increased. Three hours after the injection when the plasma level of

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[29] Fitz-Hugh, T., Jr., Pepper, D. S., and Hopkins, H. U.: The Cerebral Form of Malaria. Bull. U.S. Army M. Dept. No. 83, pp. 39–48, December 1944.

[30] See footnote 17, p. 535.

[31] Blumgart, Herrman L., and Pike, George M.: History of Internal Medicine in India-Burma Theater. [Official record.]

[32] See footnote 17, p. 535.

[33] Trager, W., Bang, F. B., and Hairston, N. G.: Relation of Plasma Level of Atabrine to Morphology and Motility of Plasmodium Vivax. Proc. Soc. Exper. Biol. & Med. 60: 257–258, November 1945.

quinacrine was falling rapidly the ratio of motile to nonmotile parasites returned to normal, and since the total parasite count did not change it was suggested the parasites had recovered after temporary damage. Similar changes during the first 3 hours after quinine at levels of 6 to 10 mg. per liter were noted. These observations emphasize the necessity for the continued serial administration of antimalarial agents in sufficient amounts and at properly spaced intervals so that adequate levels would be maintained sufficiently long to terminate clinical activity and parasitemia.

The value of single intravenous infusions of quinacrine in *falciparum* infections was studied at the 20th General Hospital.

Doses of 0.4 gm., 0.6 gm., and 0.8 gm. in 1,000 cc. of fluid were given intravenously to groups of 10 patients on each dosage schedule, and 1.0 gm. in a single infusion was given to each of 20 patients. The acute attack was terminated in all but one patient (given 0.4 gm.) without further treatment. The duration of fever in the various groups was 8 to 64 hours (average 27.2 hours) and smears became negative in from 1 to 3 days (average 2.2 days). Of the 30 patients treated with 0.8 or 1.0 gm., 19 were observed for a month or more after treatment and 4 relapsed within 3 to 5 weeks. Of the 20 patients who received 0.4 or 0.6 gm., 9 were followed for a month or more and 8 of the 9 relapsed within 10 to 23 days after termination of the attack by intravenous quinacrine. Three patients had brief periods of vomiting shortly after the infusion; one patient had a generalized convulsion; a fifth patient developed an acute state of exhilaration and excitement lasting 5 hours. Two patients with moderately severe cerebral malaria treated with 1.0 gm. of quinacrine intravenously responded well, being out of stupor in 18 hours. Twenty control patients treated for acute attacks of *falciparum* malaria with quinacrine by mouth all responded well although parasitemia and fever persisted in them a little longer than in the groups treated intravenously. In a comparison of the relative efficiency of single intravenous doses of quinine and quinacrine, it was reported that of 10 patients treated for acute *falciparum* malaria with 1.2 gm. of quinine in an infusion of 1,000 cc., the attack was terminated in only 5. The remainder continued to have high fever for 60 to 132 hours after treatment and required additional therapy. Three relapses occurred in the successfully treated group 6, 9, and 13 days, respectively, after infusion. Three patients who received single doses of 2.0 gm. of quinine in an infusion developed signs and symptoms of shock. It should be pointed out that these doses of quinine (1.2 and 2.0 gm.) are in the toxic range for this drug and are rarely if ever resorted to therapeutically. Further, a comparison of single doses of quinine and quinacrine does not take into account the rapid excretion of quinine. A more practical estimation would have been the serial administration of nontoxic amounts of quinine intravenously.

From these observations, it is apparent that although quinacrine given intravenously effectively terminates attacks of *falciparum* malaria such a procedure is not without danger and has little advantage over oral treatment in most cases. In cerebral malaria, comparably high effective plasma levels may be reached as quickly by serial intramuscular injections without the dangers inherent in intravenous therapy. Relapses, which occurred at short intervals after single doses of 0.8 or 1.0 gm. of quinacrine injected intravenously, are very common in *falciparum* infections after 2.8 gm. given in 7 days by mouth. Finally, the prompt response from intravenous quinacrine reported in Chinese patients with a high degree of immunity may not be

duplicated in nonimmune white American troops. The question of parenteral quinacrine versus quinine therapy remained unsettled.

In suppression.—The dosage of quinacrine for suppressive purposes recommended before World War II was based on evidence derived from malaria rates in various parts of the world, populated, for the most part, by immune natives. Daily doses of 0.05 gm. of quinacrine were considered inferior to a daily dose of quinine, but 0.4 gm. of quinacrine weekly in two divided doses was considered more effective than daily doses of quinine in suppressing clinical malaria.[34] Although numerous reports indicated varying success in the suppression of malaria with this divided dose of quinacrine, it was not known when we entered the war how effective such a schedule would be in nonimmune troops in highly malarious zones and under combat conditions.

Studies of the course of plasma levels resulting from 0.4 gm. and 0.6 gm. of quinacrine weekly as well as from larger amounts were conducted in England on volunteers, and in the United States on medical students[35] and at a military installation. Of 230 white soldiers observed in active training at Fort Knox, Ky., 100 men received 0.4 gm. of quinacrine weekly and another 100 received 0.6 gm. weekly. Thirty volunteers subjected to conditions simulating jungle climate were given 1.2 gm. during the first week and 0.6 gm. weekly for the next 11 weeks. It was shown that, with constant regimens, the plasma concentrations differed widely in individuals but that the group plasma level at any time was a function of the daily dose, the preexisting level, and the interval since the last dose. The group mean level rose progressively for 4 to 8 weeks to reach an equilibrium, which then remained substantially constant. The equilibrium level for the group given 0.4 gm. weekly was 1.2 μg. per liter, and was 17 for the group on 0.6 gm. weekly. It was shown that a hot, humid environment did not influence the group equilibrium level and that suppressive therapy under such environmental conditions did not affect the rate of acclimatization and performance of the men. The time for reaching equilibrium levels could be reduced from 5 to 6 weeks to 1 week by administering high initial doses for a short period (0.2 gm. daily for 5 to 6 successive days). Similar results and conclusions were reported from studies in England and civilian installations in the United States.

It was obvious that such plasma levels would give little or no protection during the first 4 to 6 weeks, or until maximum equilibrium was attained with these doses. Furthermore, marked variations in individual levels meant that the smaller weekly dosage (0.4 mg.) would frequently fail to protect significant numbers of men, especially if occasional doses were omitted. It was clearly necessary to give a large initial or priming dose before or when troops entered malarious zones in order to give immediate protection and

[34] The Treatment of Malaria; Study of Synthetic Drugs, as Compared With Quinine, in the Therapeutics and Prophylaxis of Malaria. Fourth General Report of the Malaria Commission, League of Nations, Bull. Health Organ. 6: 895, December 1937.

[35] Minutes, Subcommittee on the Coordination of Malarial Studies, 3 June 1943, National Research Council. Bulletin on Malaria Research, pp. 99–105.

prevent clinical "breakthroughs." These data were collected during the early months of 1943. Shortly thereafter, these conclusions were translated in terms of the specific recommendations for suppression of malaria contained in Circular Letter No. 153 (p. 540).

In the meantime, numerous reports from overseas had been received which documented the development of the clinical disease in large numbers of troops shortly after their arrival in malarious areas and clearly demonstrated the value of priming doses and the superiority of from 0.6 to 0.7 gm. quinacrine weekly over 0.4 gm. for suppression. Valuable information was obtained on "breakthroughs" during suppression with 0.4 and 0.6 gm. weekly and the relation of such failures to plasma levels and quinacrine discipline. Brief reference to a few field experiences to elucidate some of the factors associated with poor and successful suppression follows.

The Americal Division, which was on New Caledonia from March to October 1942, was moved to Guadalcanal during October, November, and December, where it remained until March 1943.[36] The men were forced to live and fight in hypermalarious areas with little to no field control and no mosquito repellent. Quinacrine, 0.4 gm. weekly, was prescribed but the extent of its use was not known. The malaria rates on Guadalcanal were as high as 2,500 per 1,000 per annum. The ratio of *falciparum* to *vivax* infections was 3 to 1. Following removal of these troops to the Fiji Islands and mass treatment ending on 10 June 1943, the rates in August and October were still 4,220 and 2,948 per 1,000 per annum, respectively. In September, 613 men were placed on suppressive doses of quinacrine of 0.4 to 0.6 gm. per week. The malaria rate in this group fell from 219 per 1,000 per month to 23. In November, the Division was placed on 0.4 gm. weekly and this dosage was increased to 0.6 gm. on 12 December. The malaria rate fell from 2,948 per 1,000 per annum to 80 and after 2 months' combat in Bougainville the rate in March 1944 was only 97.1. The experience in this division showed that early suppressive doses of 0.4 gm. weekly were inadequate to control malaria in combat although a moderate degree of satisfactory suppression was obtained in a nonmalarious area under fairly good disciplinary conditions. On the other hand, 0.6 gm. of quinacrine proved highly effective both in malarious areas and in regions free from malaria (chart 29). Another example was the 43d Division, which had also been on 0.4 gm. weekly with a high incidence of malaria. Half the division was taken off suppression and had a malaria rate of 2,000 per 1,000 per annum. The other half was placed on 0.6 gm. weekly and their rate fell to 236 per 1,000 per annum. Again, a naval construction battalion of 840 men, on a suppressive regimen of 0.4 gm. weekly, arrived on Guadalcanal on 12 December 1942.[37] During the first 5 weeks, 123 men were down with malaria, about 95 percent of which was due to *P. falciparum*. In the same report it was stated that two combat infantry outfits on 0.4 gm. weekly entered a highly malarious area and within 2 weeks malaria was occurring at the rate of 40 to 60 cases a day, most of them caused by *P. falciparum*.

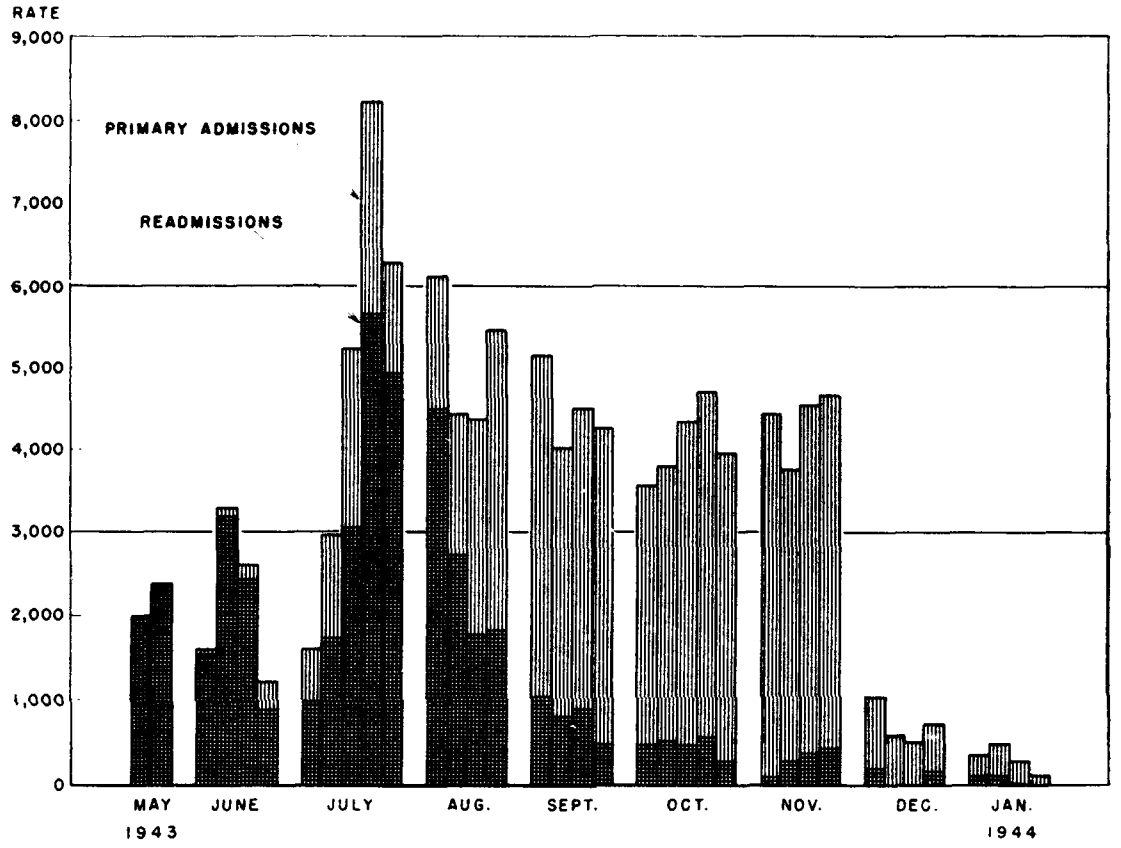
Although the great majority of initial infections in the Pacific islands were caused by *P. falciparum*, subsequent relapses were principally caused by *P. vivax*. When adequate amounts of quinacrine were used in termination of the attack of *falciparum* malaria and when suppressive medication of 0.1

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[36] Essential Technical Medical Data, South Pacific Area, for April 1944.
[37] Lewis, R. A.: The Suppression of Malaria. [Official record.]

CHART 29.—*Malaria rates in an infantry regiment under various schedules of suppression with quinacrine hydrochloride, by week*

[Rate expressed as number of attacks per annum per 1,000 average strength]



gm. daily was continued, *falciparum* malaria rarely occurred on discontinuance of suppression.

In the Australian studies that have been referred to,[38] it was conclusively shown in volunteers infected with *P. falciparum* (New Guinea strain) transmitted by mosquitoes that, if 0.1 gm. of quinacrine were administered during the period of infection and for 23 days after the last infective bite, clinical malaria did not occur during suppression or after its termination. Actual cure was demonstrated by subinoculation of 200 cc. of blood into other volunteers. If subinoculation was done on the 9th to 11th days after infection, malaria developed in the recipients, indicating that quinacrine was not a causal prophylactic but effected a cure by permanently destroying the erythrocytic parasites after their appearance in the blood. Similar studies in England and in this country with other strains of *P. falciparum* also demonstrated the curative action of quinacrine suppression in such infections. In the Australian experiments along the same lines with *P. vivax*, there was shown complete clinical suppression during therapy but no curative effect, for all the volunteers developed *vivax* malaria at varying intervals after quinacrine was discontinued.

The practical inferences from these observations were that effective plasma equilibrium having been established, quinacrine administered in doses

[38] See footnote 12, p. 529.

of 0.1 gm. daily without interruption would effectively suppress both *falciparum* and *vivax* malaria and that, if suppression were continued for about 3 weeks in troops leaving the malarious area, *falciparum* malaria would not develop. *Vivax* relapses would occur later and could be effectively terminated with quinacrine or delayed indefinitely if necessary by continued suppression. These results were seen in many studies overseas and in this country.

In one experiment, for example, 107 volunteers were taken to a highly malarious area in New Guinea where they were exposed to infection for 44 days. Initial priming doses were followed by 0.1 gm. of quinacrine daily administered 6 days a week during the period of exposure and for 10 days thereafter. No case of malaria developed during the period of suppression, whereas of 44 men who acted as controls and received no medication, 32 developed malaria (in 9 caused by *P. falciparum*). Subsequent to the discontinuance of suppressive therapy 25 cases of malaria due to *P. vivax* developed. No case of malaria caused by *P. falciparum* developed in the group receiving quinacrine either during or after suppressive treatment. This field study showed definitely the value of quinacrine in absolutely preventing clinical malaria due to *P. vivax* and *P. falciparum* during adequate suppression and the curative as well as suppressive action of quinacrine in *falciparum* infections.

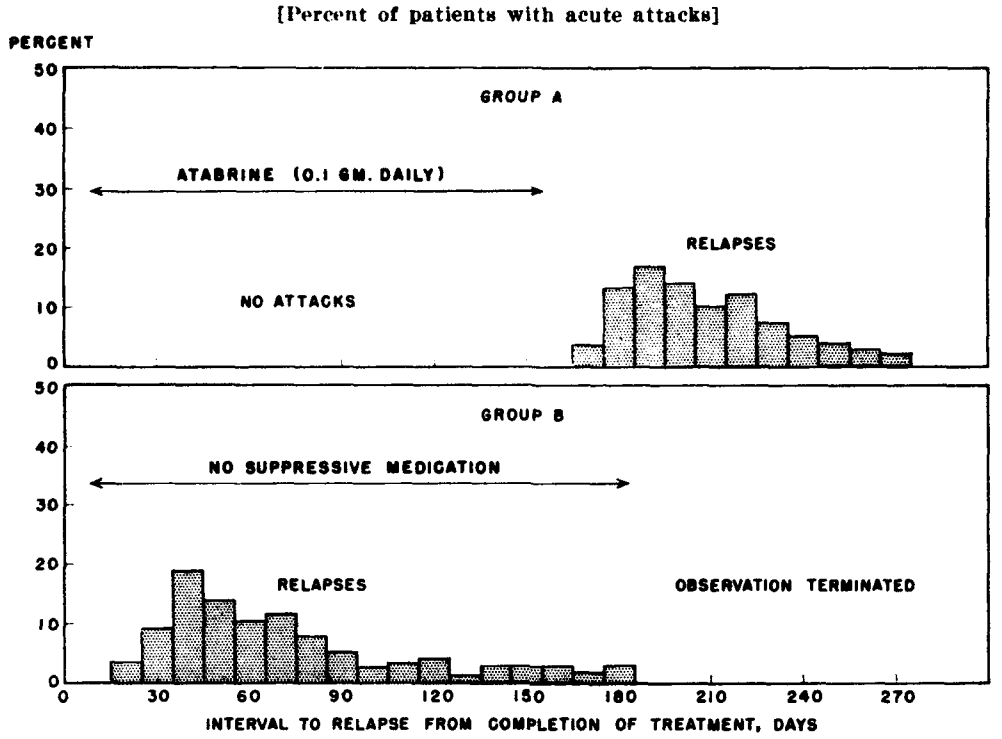
In general, the plan of suppression with doses of 0.1 gm. daily was widely used with excellent results. In one oversea area, it was suggested that troops on patrol or in combat may fail to take occasional doses. Studies with single doses of 0.4 or 0.5 gm. twice a week carried out in the field showed that such a schedule would provide adequate protection and insure affective levels all the time.[39] This modified plan was not generally adopted but could be used under circumstances precluding regular daily suppressive medication.

By continuing quinacrine therapy for suppression following termination of acute attacks of *vivax* infections, it was possible to maintain effective fighting strength in combat units highly seeded with malaria. In this country, continued suppression for 3 months or more reduced the number of hospital admissions for relapses without interrupting training or rehabilitation programs. At one hospital in the United States, for example, 79 men treated with 2.8 gm. of quinacrine in 7 days for acute attacks of *vivax* malaria of Pacific origin were maintained on 0.1 gm. daily for 150 days after termination of the acute attack. No parasitemia or clinical attack occurred during the 5 months of suppression. In a similar sized group, also treated for acute attacks but not subsequently placed on suppressive therapy, 80 percent relapsed during the first 120 days' observation after treatment. The group given effective protection during 5 months by continued therapy was not thereby protected against subsequent relapse, for 82 percent relapsed during the 120-day period of observation after discontinuance of suppression (chart 30).

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[39] Duncan, G. G.: Quinacrine Hydrochloride as a Malaria-Suppressive Agent for Combat Troops. War Med. 8: 305–318, November-December 1945.

CHART 30.—*Distribution of relapses in two groups of patients after treatment for acute attacks of* vivax *malaria of Pacific origin*



The subject of "breakthroughs" or clinical attacks during suppression received attention at many oversea installations. In India, six patients supposedly taking 0.1 gm. of quinacrine a day were admitted to the 20th General Hospital and found to have plasma levels of 6, 7, 8, 12, 12, and 14 μg. per liter, respectively. In every case, it was possible to show that the individual was able to absorb quinacrine normally, the reason for the low levels being failure to take the prescribed dose daily. In the Southwest Pacific, 80 percent of 116 men who had attacks while on suppression were found to have levels of less than 10, whereas only 25 percent of another group of 853 men had similarly low levels. Seventy-five officers having attacks while supposedly taking 0.1 gm. quinacrine daily were found to have low plasma levels and admitted not taking the drug regularly. On the other hand, four men with acute attacks were found to have levels of from 16 to 30 μg. per liter when admitted. It is possible that self-administered medication for beginning symptoms may account for apparently adequate levels in some "breakthroughs." In a division in the Southwest Pacific, the average level for 1,021 men on suppression for a year or more was 13 μg. per liter and varied from an average of 5 in men who "broke through" to an average of over 20 in companies with good discipline.[40]

[40] Schaffer, A. J., and Lewis, R. A.: Atabrine Studies in the Field. I. Relation of Serum Atabrine Level to Breakthrough of Previously Contracted Vivax Malaria. Bull. Johns Hopkins Hosp. 78: 265–281, May 1946.

Toxicity

Effects of prolonged administration

Toxic reactions, principally related to the gastrointestinal tract and nervous system, associated with the ingestion of quinacrine or its parenteral use had been reported before World War II. In an analysis of toxic reactions observed in 49,681 patients to whom quinacrine had been administered before 1941, it was concluded that neurogenic symptoms (headache, mental depression, delirium, psychoses, convulsions) occurred rarely (less than 1 per 1,000) and that gastrointestinal symptoms (nausea, vomiting, diarrhea) were uncommon and of little significance and were frequently related to the concomitant administration of other drugs. More serious reactions were poorly documented and could not be unequivocably related to quinacrine.

Following our entry into the war and the extensive use of quinacrine over prolonged periods for suppression and frequently for termination of acute attacks with larger amounts of drug than were previously used for either purpose, great interest was stimulated in the potential acute or chronic toxic effects of such medication. No attempt will be made in this section to review the voluminous studies made with various experimental animals. Brief reference will be made to observations on the effects of quinacrine not previously reported or to findings that were of significance during World War II.

Liver and kidneys.—Studies of hippuric acid synthesis, serum phosphatase, urea clearance, and liver biopsies (10 cases) performed on 101 men who had been on suppression from 8 to 36 months revealed no abnormalities. Similar negative findings resulted from detailed examinations of liver and kidney function of 43 Oxford University undergraduates who took 0.1 gm. of quinacrine daily over a period of 9 to 12 months.

Studies to discover subclinical hepatic damage in white and Negro American troops who had been taking 0.6 gm. quinacrine weekly for 18 to 24 months were done on various groups of 50 men. The icteric index, urinary urobilinogen, sulfobromophthalein excretion, fibrinogen, galactose tolerance, and cephalin-cholesterol flocculation tests failed to detect any evidence of subclinical hepatic dysfunction.[41] On the other hand, there were a few reports of varying degrees of liver disease believed related to quinacrine ingestion.

Four cases of hepatic dysfunction (two subclinical and two severe hepatitis, one of which ended fatally) believed related to quinacrine were reported from an oversea theater. An interesting feature in these cases was the association of corneal edema, manifested by blurred vision. In three of the patients corneal edema became less marked after discontinuance of quinacrine and was aggravated by its readministration. Impaired liver function did not become apparent until 3 to 6 months after the initial episode of visual disturbance. The observers of these patients felt that corneal edema and

[41] Gottfried, S. P., and Levine, A. C.: Liver Function Studies on Soldiers Under Prolonged Atabrine Administration. J. Lab. & Clin. Med. 30: 853–855, October 1945.

punctate erosions of the surface epithelium were due to quinacrine, that this was a rare manifestation of quinacrine toxicity, and that its occurrence may be followed by liver disease.

In a large series of Chinese patients receiving quinacrine for suppression or treatment of malaria there were 5 with severe hepatitis and exfoliative dermatitis, 3 of whom died of this complication (incidence 1 in 2,000–3,000 Chinese).[42] The rash present in each case appeared as early as the 2d day and as late as the 10th day of medication and consisted of a scarlatiniform, maculopapular, dry, scaling eruption beginning on the face and involving the entire body. Conjunctivitis and exfoliation of the tongue were observed. Jaundice, which appeared several days after the rash, was accompanied by a high ("septic") fever, leukocytosis, proteinuria, and bilirubinuria. The liver was large and tender at first but shrank rapidly. Mental clouding was prominent and death followed in coma in the third to fifth week of the disease. At autopsy there was gross and microscopic evidence of severe hepatitis or necrosis of the liver. It was concluded that quinacrine in previously sensitized individuals was responsible for both the hepatitis and the severe dermatitis.

Aplastic anemia.—A small number of cases of aplastic anemia with and without atypical lichen planus had been reported from the Pacific area, and this was thought to be possibly ascribable to quinacrine. In an attempt to determine whether prolonged use of quinacrine was responsible for the production of pathological changes in the body, the Army Institute of Pathology (now the Armed Forces Institute of Pathology), Washington, D.C., instructed laboratory officers to furnish data of quinacrine ingestion with all autopsy protocols, regardless of the cause of death. For some time, nothing of significance was observed. Later, it became apparent that aplastic anemia was the cause of death in a disproportionately large number of cases represented by autopsy material sent from the South and Southwest Pacific Areas where an extensive regimen of quinacrine suppression was in force. Fifty-seven cases of aplastic anemia were the basis of a report[43] on the possible relation of this disease and quinacrine. The incidence of aplastic anemia per 100,000 men varied little (0.1 to 0.3) from 1942 to 1945 in the continental United States and all foreign theaters, exclusive of the South and Southwest Pacific Areas and the China-Burma-India theater, where it rose from zero in 1942 to a peak of 2.84 per 100,000 during the last 6 months of 1944. Quinacrine was the common drug in at least 47 cases, 9 others being excluded because of the possible role of arsenic, irradiation, or sulfonamides in the production of the aplastic state. In the group treated principally with quinacrine, the drug had been taken for a period of from 1 to 34 months; in the majority, from 4 to 9 months. Large doses were specifically reported in six cases. Four patients had increased the daily dose to 0.2 gm. for a period of from 3 weeks to 8 months; one patient took 20 to 30 tablets during 4 days before onset of symptoms and another was said to have ingested "massive doses" for 3 weeks before he became sick. Hepatitis was present in 10 cases

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[42] Agress, C. M.: Atabrine as a Cause of Fatal Exfoliative Dermatitis and Hepatitis. J.A.M.A. 131: 14-21, 4 May 1946.

[43] Custer, R. P.: Aplastic Anemia in Soldiers Treated With Atabrine (Quinacrine). Am. J.M. Sc. 212: 211-224, August 1946.

and the "quinacrine dermatitis complex" in 25. The liver lesions in five cases were indistinguishable from epidemic hepatitis. Cerebral hemorrhage was the immediate cause of death in 10 cases. The bone marrow in all cases was badly depleted of normal hematopoietic elements, often almost totally so without evidence of extramedullary hematopoiesis. Occasionally, the influx of lymphocytes, plasmocytes, and histiocytes attained such proportions that at first glance the fundamental hypoplastic state was not apparent. One man who received 65 transfusions and lived 10 months had extensive secondary fibrosis of the marrow cavity. Clinically, the onset was gradual in most cases, and purpuric manifestations were commonly seen early. In many cases, the red blood cell count could be maintained at fairly good levels by repeated transfusions, but the white cells and platelets remained uniformly depressed. In 20 cases, the "quinacrine dermatitis complex" preceded the anemia. Although this form of possible quinacrine toxicity has proved fatal in the great majority of cases, recovery has been reported.[44]

Asymptomatic changes in the skin.—Changes in the skin and mucous membranes resulting from the prolonged administration of quinacrine were the subject of numerous reports. They varied from asymptomatic pigmentary changes to severe and disabling forms of dermatitis.

The yellow discoloration of the skin associated with quinacrine ingestion was a common finding in the majority of men on prolonged suppression. The intensity of the discoloration, which is not a toxic manifestation of drug ingestion but rather an expression of its deposition in the skin, varied with duration and dosage of suppression, exposure to sunlight, and complexion, being most marked in subjects with dark skin and hair.

Attempts were made to correlate the degree of fluorescence produced by quinacrine in the skin and plasma levels with the use of a dermofluorometer. A high degree of correlation of induced palmar skin fluorescence with mean plasma levels was found in 33 volunteers on 0.2 gm. daily for 1 week and 0.1 gm. daily for 3 weeks. The peak of fluorescence in the skin was reached in 4 to 5 weeks after initial dosage and decreased slowly over a 12-week period after the drug was discontinued. It was believed that this instrument might be useful in the field in determining whether quinacrine suppression discipline was effective.

Quinacrine discoloration of the sclera, as observed in a small number of individuals, was described[45] as consisting of yellowish pigmentation, most marked around the limbus in the part of the sclera exposed in the palpebral fissure, and fading toward the fornices. On the other hand, in jaundice, the pigmentation is most marked in the fornices toward the equator of the globe and fading toward the limbus.

Ochronosis-like pigmentation of mucous membranes, skin, and cartilage was described in many individuals on quinacrine suppression. In a dental

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[44] Most, H., and Hayman, J. M., Jr.: Recovery From Severe Hypoplastic Anemia Associated With Atypical Lichen Planus. Bull. U.S. Army M. Dept. 5: 339-342, March 1946.

[45] Hayman, J. M., Jr.: Atabrine Pigmentation of the Sclera. Bull. U.S. Army M. Dept. No. 82, pp. 120-121, November 1944.

survey of 1,000 men in the Philippine Islands, 300 showed bluish-purple pigmentation of the hard palate. The color varied from a light blue purple to intense blue black involving from 1 cm. to the entire palate.[46] In another report,[47] the incidence in 500 men in the Southwest Pacific Area was 31 percent. The majority of the men with pigmentation of the palate had been on quinacrine suppression for at least 7 months. The nature of the pigment based on staining reactions of biopsy sections was considered to be hemosiderin. A detailed study of a small number of patients showed the ochronosis-like pigment to be distributed in the skin, hard palate, nail beds, the cartilages of the nose, ears, epiglottis, and trachea, the conjunctivae and corneoscleral limbus. Phenol and alkaptonuria were excluded as causative factors. Surveys at Harmon General Hospital, Longview, Tex., and Moore General Hospital, Swannanoa, N.C., likewise demonstrated an incidence of 15 to 30 percent of asymptomatic pigmentation as described above in patients who had been on prolonged quinacrine suppression overseas.

Atabrine dermatitis complex.—More significant changes in the skin were reported from overseas as causing disability and frequently serious prolonged illness. For security reasons and in order to maintain the morale of quinacrine suppression, the data accumulated were not made generally available at first. It was necessary in the beginning to collect information on the incidence of these reactions and to evaluate fully the relation of quinacrine to them. The possibility of substituting another suppressive agent for quinacrine had to be considered if this cutaneous complex proved to be widespread or if unfounded rumors as to its incidence and severity threatened a breakdown in discipline. Fortunately, this did not occur nor was it found that the incidence of the Atabrine dermatitis complex was very great. The following paragraphs from a report entitled "Evaluation of the Untoward Reactions Attributable to Atabrine" prepared by the Medical Consultants Division of the Surgeon General's Office[48] summarize the vast amount of clinical and other data collected overseas and in this country:

> Medical officers in the Southwest Pacific Area called attention, in the latter part of 1943, to a characteristic cutaneous syndrome which was occurring in soldiers who had been evacuated from New Guinea and adjacent islands. Lt. Col. Charles L. Schmitt, MC, and Maj. (later Lt. Col.) Thomas W. Nisbet, MC, dermatologists stationed with general hospitals in that area, were the first to submit to The Surgeon General official reports in which they described the disease and its probable etiology. Later, similar cases were reported from all other theaters where suppressive atabrine medication was in general use as a control measure for malaria. This syndrome has been observed most frequently in New Guinea and adjacent islands and in Assam and northern Burma; in other areas only small numbers of cases have occurred.

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[46] Summer, S.: An Oral Manifestation of the Use of Atabrine. [Official record.]

[47] Lippard, V. W., and Kauer, G. L., Jr.: Pigmentation of the Palate and Subungual Tissues Associated With Suppressive Quinacrine Hydrochloride Therapy. Am. J. Trop. Med. 25: 469-471, November 1945.

[48] Evaluation of the Untoward Reactions Attributable to Atabrine. Bull. U.S. Army M. Dept. 4: 653-659, December 1945.

This skin disease which has acquired the name atypical lichen planus is characterized by various * * * types of lesions. * * * Almost all patients have both violaceous, hypertrophic lichenoid plaques and some form of cutaneous eczematoid reaction. During the course of the disease, a considerable number of these patients have acute, "explosive" generalized exacerbations, manifested by oozing eczematoid dermatitis having a predilection for the flexors, groins, axillae, extremities, and neck. Such exacerbations resemble exfoliative dermatitis * * * which is as severe as the cases of primary exfoliative dermatitis described below. The seriousness of such a state and the need for expert management of these patients cannot be overemphasized.

Usually the disease is characterized by the onset of localized violaceous or erythematous eczematoid plaques * * * followed by generalization of the lesions with subsequent appearance of the lichenoid plaques and mucous membrane lesions. * * * Any part of the cutaneous surface may be involved, but there is a predilection for the lower legs, forearms, dorsal surface of hands and feet, face, buttocks, lower anterior surface of the neck, genitalia, mucous membranes of the mouth, eyes, and eyelids. Residual effects and lesions which develop later in the course of the disease include: atrophy; hyperpigmentation (melanin) and depigmentation; diffuse follicular accentuation over the upper back, shoulders, and extremities; changes in the nails; moth-eaten, patchy alopecia; and marked disturbance in sweating function.

* * * A characteristic type of eczematoid dermatitis which also has occurred in individuals taking suppressive Atabrine * * * is characterized by bilateral, symmetrical, violaceous-tinged, vesicular, eczematoid and oozing plaques involving the hands, arms, feet, legs, and sometimes other parts of the body. Secondary pyogenic infection is common. The nail bed and skin of the nail folds are usually involved, frequently resulting in exfoliation of the nails without true suppurative paronychia. With experience, on clinical grounds, one can in most cases distinguish between this eruption and other forms of eczematoid dermatitis. Tentatively the term "symmetrical eczematoid dermatitis" has been used * * *.

It does not seem advisable to make a sharp distinction between the so-called atypical lichen planus and the symmetrical eczematoid dermatitis syndrome. From a broad point of view, it seems that all of these patients have either a lichenoid cutaneous reaction or an eczematoid cutaneous reaction or a combination * * *. A small percentage of the total group have lichenoid lesions alone; a larger group have a combination of lichenoid and eczematoid lesions; and a still larger group have eczematoid lesions that are not accompanied by lichenoid lesions.

* * * reports of general Army experience * * * indicate that Atabrine is the essential etiological factor. The mechanisms resulting in the lichenoid reaction and the eczematoid reaction are probably different. For example, it was observed in a carefully controlled series of cases at Moore General Hospital that the time interval preceding exacerbations of eczematoid lesions is much shorter than with the lichenoid lesions. The fact that the incidence has been so very much higher in New Guinea and adjacent islands and in Assam and northern Burma suggests that climatic or geographic factors may play a contributory role in the etiology. There is evidence that various forms of cutaneous trauma may contribute to the onset and localization of the lesions, particularly the eczematoid phase of the eruption. The sequence of events in many cases suggests that individuals taking suppressive Atabrine have a tendency to acquire chronic eczematoid dermatitis on contact with external allergens (such as certain jungle plants and trees) rather than self-limited contact dermatitis which is the usual course * * *. It appears that cutaneous reactions are more frequent in individuals who have been taking Atabrine in dosages above the recommended suppressive amount (0.7 gm. per week). It should be emphasized that the incidence of these cutaneous diseases has been relatively low, even in New Guinea, and, from the military point of view, has not been an important handicap.

Since available evidence indicates that we are dealing with one complex, it is suggested that it would be best to group these cutaneous reactions attributed to Atabrine under one heading "Atabrine dermatitis complex" and classify the various manifestations as follows: (1) lichenoid dermatitis; (2) lichenoid and eczematoid dermatitis (both including cases heretofore referred to as "atypical lichen planus"); (3) eczematoid dermatitis (including cases heretofore referred to as "symmetrical eczematoid dermatitis"); (4) exfoliative dermatitis secondary to (1), (2), or (3).

The treatment of these conditions depends for the most part on early recognition of the trouble and discontinuation of Atabrine. In many instances, it is difficult to decide whether or not a given case of eczematoid dermatitis is due to Atabrine. It is necessary to study such cases carefully, with careful observation after withdrawal of Atabrine and possibly cautious trial readministration of the drug (do not attempt readministration of Atabrine to a patient who has had exfoliative dermatitis or a severe generalized eczematoid exacerbation). * * * When possible, such patients should be seen by a competent dermatologist, and every effort should be made to rule out other etiological factors. Parenteral administration of penicillin is indicated in patients with secondary pyogenic infection. Local treatment should be bland and nonirritating, and should consist of preparations such as 1:9,000 potassium permanganate soaks, Burow's solution soaks, 5 percent aqueous solution of tannic acid spray for oozing intertriginous sites, and application of borated cold cream if a grease is indicated. Preparations such as salicylic acid ointment, tincture of iodine, and sulfonamide ointments should not be used. Arsenicals and bismuth have been tried in some cases without affecting the course significantly; they should not be used. Superficial X-ray therapy, if indicated, should be used only under the direction of a competent dermatologist and in small doses (not more than 75 r and not to exceed a total of more than 375 r to 450 r). At least some of these patients have some degree of light sensitivity. Therefore, exposure to sunlight should be avoided and ultraviolet light therapy should not be used. All patients should be studied from the general medical standpoint, including studies of blood, serum proteins, and liver function. Therapeutic agents such as plasma, liver extract, multiple vitamins, and intravenous glucose should be used when indicated.

The prognosis varies from individual to individual. In general it is excellent, especially if the patient is hospitalized early in the course of the disease * * *. The lichenoid lesions involute slowly, but they do not tend to recur; the eczematoid phase of the eruption may involute rapidly, but it tends to recur and is responsible for the prolonged disability which occurs in some cases. In general, recovery is a matter of weeks and months. Residual hyperpigmentation, depigmentation, and atrophy at the sites of lesions become less pronounced as time goes on and the hypohidrosis which occurs in many patients also improves spontaneously. The course is usually prolonged in all cases of exfoliative dermatitis because of frequent exacerbations. It should be noted that these patients have not been followed for a sufficient length of time to make final statements in regard to the prognosis of these cutaneous reactions.

Another major type of cutaneous reaction which has been attributed to Atabrine is primary exfoliative dermatitis, not secondary to the lichenoid-eczematoid syndrome. This is characterized by acute fulminating exfoliative dermatitis, demonstrably associated with true hypersensitivity to Atabrine. It is in every respect similar to exfoliative dermatitis due to other agents such as arsenicals. This type of cutaneous reaction * * * is believed to be associated with Atabrine, much less commonly with quinine. Hypersensitivity of this degree may constitute a dangerous state in either instance.

Acute reactions to short-term administration

The principal toxic manifestations from therapeutic amounts of quinacrine usually employed in terminating acute attacks of malaria or from small

initial doses early in suppression are related mainly to the skin, gastrointestinal tract, and central nervous system.

Skin.—Acute reactions in the skin related to hypersensitivity or reactivation of eczematoid dermatitis following small amounts of quinacrine have been discussed. In addition, urticaria and pruritus have been described as an uncommon toxic manifestation of quinacrine ingestion. In a report[49] from India, 12 cases of pruritus and urticaria, particularly of the palms, were described in the course of quinacrine suppression. In 2 patients, symptoms began within 3 days after suppressive medication was started and, in the other 10 patients, within 2 to 3 weeks. The symptoms subsided in three patients while they were still on the drug and in nine within 4 days after the drug was discontinued. Six patients had no recurrence when quinacrine was readministered, and, in the three who had a recurrence, symptoms disappeared with continued medication.

Gastrointestinal tract.—Gastrointestinal symptoms (*nausea and vomiting*) are rarely encountered with quinacrine during therapeutic termination of acute attacks of malaria. Frequently, these symptoms when present are due to malaria rather than to ingestion of the drug. The administration of quinacrine in colored capsules to patients who stated they could not take it because of gastrointestinal symptoms completely forestalled the development of such symptoms.[50] Likewise, giving the drug after meals or with sweetened *fluids during an attack of malaria* reduced the incidence of nausea. Nausea, vomiting, and diarrhea were reported in large numbers of men on initial suppressive doses of 0.2 gm. twice weekly in some series and not at all in others. Symptoms usually disappeared after three or four doses and occurred only infrequently in the 0.1 gm. daily schedule. Psychological factors, field sanitary conditions, and other reasons were held mainly responsible for gastrointestinal symptoms. The consensus was that these reactions were never severe and almost invariably disappeared if the drug was continued.[51]

Central nervous system.—Before World War II, mental disturbances were reported as occurring in approximately 1 to 2 of every 1,000 cases of malaria treated with quinacrine orally or intramuscularly, and various aberrations of the central nervous system attributed to quinacrine were reported in a number of cases during the war.

In 7,604 patients treated with quinacrine in a period of 7 months at an oversea general hospital, 35 cases of toxic psychosis were observed.[52] Total doses of 2.1 gm. quinacrine in a week were routine. The greatest number of reactions occurred within 6 days of completion of therapy, although one was observed after only 0.9 gm. had been given and one developed as late as 12 days after therapy. There were two main types of onset. The most frequent

[49] Essential Technical Medical Data, India-Burma Theater, for August 1945, inclosure 3 thereto.

[50] See footnote 15 (1), p. 532.

[51] The Drug Suppressive Treatment of Malaria. Bull. U.S. Army M. Dept. No. 73, pp. 29-34, February 1944.

[52] Gaskill, H. S., and Fitz-Hugh, T., Jr.: Toxic Psychoses Following Atabrine. Bull. U.S. Army M. Dept. No. 86, pp. 63-69, March 1945.

(65 percent) was marked by excitation, hallucinations, and delusions. The other (35 percent) began with retardation, disorientation, and amnesia for recent events together with confabulation. No constant physical or laboratory findings were obtained. The course of the psychosis was benign in most instances. Sixteen patients were subsequently (after 16 to 210 days) retested with quinacrine and only one showed any untoward reaction, consisting of mild excitement which cleared within 24 hours. There was no evidence that the men who developed toxic quinacrine psychoses were unstable psychologically. Two patients who did not recover developed typical schizophrenic reactions. There was no evidence of latent psychosis in the previous behavior of these two patients. Treatment consisted of restraint, sedation, supervision, and nursing care. The authors believed that the psychoses represented a quinacrine sensitivity reaction following which there was an unreactive period.

In another report from overseas,[53] 28 cases of quinacrine psychosis were observed in the Americal Division. The degree of malarial infection and the great number of relapses treated in this division would indicate the incidence of this reaction to be extremely low. Two patients gave a history of previous psychotic reactions to quinacrine, and in two additional patients it was believed that schizophrenia was induced by the drug. Only one case was noted during the standard course of 2.8 gm. of quinacrine in 7 days. The remainder developed during or after larger total doses, 18 patients receiving more than 3 gm. Confusion was the prominent clinical feature of the psychosis in 27 patients. Hallucinations occurred in eight cases. Recovery was complete within 10 days in 16 patients. By the use of the Koh's block test, these authors showed that there was evidence of confusion in 7 of 31 patients treated with 4.5 gm. quinacrine during 9 days, while no such changes could be demonstrated in 27 patients treated with 2.1 gm. in 7 days. Additional cases of quinacrine psychosis were reported from various installations overseas and in the United States, but their incidence was an insignificant fraction of the total number of psychoses that occurred in the U.S. Army.

Convulsions were reported in six patients treated with "massive" amounts of quinacrine orally[54] and in two who were treated intravenously. The convulsions occurred during treatment or on the following day, with unconsciousness for 5 to 15 minutes followed by confusion. Within 24 hours, these patients were all mentally clear. Plasma levels determined in three cases were from 180 to 280 μg. per liter. Studies were stimulated by observation of high plasma levels with parenteral quinacrine therapy and by reports in the literature before World War II[55] of mental changes associated with parenteral medication. A group of 13 volunteers were given 0.9 gm. of quinacrine

[53] Newell, H. W., and Lidz, T.: The Toxicity of Atabrine to the Central Nervous System. I. Toxic Psychoses. Am. J. Psychiat. 102: 805-818, May 1946.

[54] Newell, H. W., and Lidz, T.: The Toxicity of Atabrine to the Central Nervous System. II. Convulsions. Am. J. Psychiat. 102: 805-818, May 1946.

[55] See footnote 34, p. 545.

daily for 7 days. Peak plasma levels were from 156 to 420 with a mean of 286 μg. per liter. No symptoms or signs related to the nervous system were observed. Electroencephalographic studies revealed only small and inconsistent changes not characteristic of those observed in convulsive disorders of the brain. In another study, five normal subjects were given sufficient quinacrine by mouth during 7 to 10 days to produce plasma levels in excess of 100 μg. per liter. In all cases, there was evidence of marked psychologic stimulation (motor acceleration, restlessness, sleeplessness, and increased capacity for work), and the electroencephalogram showed a significant shift toward faster frequencies. These manifestations appeared by the third day and persisted for 6 to 8 days after the drug was discontinued. The authors considered the data convincing evidence that quinacrine acted as a cortical stimulant.

Summary of Studies

An experimental approach to the chemotherapy of malaria led to a rational use of quinacrine for effective treatment of attacks and for suppression. The development of chemical methods for estimating quinacrine in biological fluids and tissues resulted in a better understanding of the limitations of treatment and suppressive schedules in use before and early in World War II. Clinical and field studies carried out on a large scale demonstrated that quinacrine if properly used was superior to totaquine or its component alkaloids for treatment or suppression of malaria due to *P. vivax* or *P. falciparum*. Quinacrine produced more prompt control of fever, symptoms, and parasitemia; was less toxic; and provided a longer interval to relapse than quinine, sulfonamides, or heavy metals. Quinacrine was shown to induce definitive cure in *falciparum* infections and to provide effective suppression of relapsing malaria when priming initial doses were followed by daily doses of 0.1 gm. Failures in suppression (breakthroughs) were shown mainly due to poor discipline and failure to take the drug. Parenteral use of quinacrine was found effective in severe *falciparum* infections, but no conclusive comparative study was reported between quinine and quinacrine given parenterally. Toxic reactions known before the war were encountered, these consisting of minor gastrointestinal symptoms and toxic psychoses. In addition, prolonged quinacrine ingestion produced edema of the cornea in some cases, and in a large number of cases, the following reactions were described: (1) Ochronosis-like pigmentation of skin, mucous membranes, and cartilage (possibly with hepatitis), (2) urticaria and, more significantly, a dermatitis complex (atypical lichen planus and/or eczematoid dermatitis), and (3) aplastic anemia. It was only shown that long-continued suppression produced these reactions in only a small proportion of men taking the drug and that on the whole no significant disturbances in organ function resulted. The proper use of quinacrine made possible effective military operations in highly malarious areas.

4-AMINOQUINOLINE COMPOUNDS

The background for the elaboration and study of this group of compounds is reviewed in a report on investigations of potentially antimalarial drugs in the laboratories of the I. G. Farben Werke in Elberfeld, Germany. Following the discovery, in 1924, of Plasmochin (a trade name for pamaquine naphthoate, an 8-aminoquinoline) interest was centered on the possibilities of quinoline derivatives. A total of 314 acridine derivatives were prepared, but none was found to be more active than quinacrine. In 1929, work with the 4-aminoquinoline compounds was begun, and in 1934 a compound as effective as quinacrine was discovered and furnished the impetus for the preparation of numerous derivatives during the years following. Although this information was not available to us during World War II, it is of interest that two reports appeared in the French literature which discussed very generally the antimalarial properties of Sontochin (SN 6,911), one of the 4-aminoquinoline drugs prepared in Germany.

This drug became available in North Africa during the Second World War, and its chemical identity was established. It was subsequently synthesized and made available to the U.S. Army for experimental and clinical testing. A brief discussion of the antimalarial properties of Sontochin is presented, to be followed in turn by brief discussions of several other derivatives prepared in this country, particularly SN 7,618 or Chloroquine Diphosphate, which proved to be the most effective. The proper uses of Plasmochin, rediscovered during the war, will be discussed in due course.

Sontochin (SN 6,911) [56]

General properties

Absorption of the bisulfate of SN 6,911 is essentially complete whereas only about 80 percent of the binaphthoate is absorbed. Following its absorption, the drug is extensively localized in the tissues. About 25 percent of the daily dose is excreted; about 75 percent is degraded. The plasma level falls approximately 25 percent per day. Daily doses of 0.3 gm. of base result in mean plasma levels of 160 μg. per liter (range 66 to 292). Therapeutic effects in *vivax* infections, that is, control of fever and parasitemia without recurrence within 14 days, are obtained with mean plasma levels above 80 μg. per liter for 4 days and, in *falciparum* infections, with levels of 110 to 200 μg. per liter for 6 days. A therapeutic schedule consisting of 0.9 gm. on the first day and 0.3 gm. daily for 3 additional days produces plasma levels of from 125 to 193 μg. per liter for 4 days and is effective in terminating induced *vivax* and *falciparum* infections.

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[56] Formula: 3-Methyl-7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline bisulfate or binaphthoate.

Clinical testing

Acute attacks.—The relative efficiency of SN 6,911 and quinacrine in the treatment of acute attacks of *vivax* malaria of Pacific and Mediterranean origin was studied at Harmon General Hospital. A total of 99 patients were treated with 3.2 gm. of SN 6,911 base during 7 days. There was prompt control of fever and symptoms (86 to 100 percent fever free on the second day), but not significantly more so than with quinacrine, and parasites disappeared from the blood at approximately the same rate with either drug. Of 75 patients followed for at least 60 days after completion of treatment, 49 (about 65 percent) relapsed; the interval to relapse was snorter, 27 percent occurring in the first 5 weeks after treatment with SN 6,911, compared with only 7 percent in the same interval after treatment with quinacrine. In this study, no advantage of SN 6,911 over quinacrine was found.

From similar observations in studies carried out at various U.S. naval installations, similar conclusions were drawn. Single doses of 1.0 gm. SN 6,911 were found effective in terminating acute attacks of *vivax* malaria of Pacific origin in 45 patients. Parasitemia was controlled within 36 hours, and usually no further paroxysms occurred. Relapses were observed in as little as 24 days after therapy. Toxic symptoms or signs were not encountered.

No extensive studies on treatment with SN 6,911 for malaria caused by *P. falciparum* were carried out in the field. In India, it was shown that a single infusion of 0.64 gm. of SN 6,911 in 1,000 cc. of saline given intravenously during 2 to 3 hours was effective in terminating acute attacks of *falciparum* malaria. Twenty Chinese soldiers were so treated, and within 1 to 4 days (average 2.5 days) blood smears became negative. Fever was controlled in 12 to 80 hours (average 41 hours). The response was comparable to that observed in 20 patients who were given 0.6 gm. of quinacrine intravenously although the latter became fever free on the average of 12 hours sooner than those treated with SN 6,911. In the United States, it was shown that 0.9 gm. of SN 6,911 administered for 1 day followed by 0.3 gm. daily for 6 days effected definitive cure in induced *falciparum* infections.

Suppression.—Studies with SN 6,911 were carried out in Australia on volunteers infected by mosquitoes with the New Guinea strains of *P. vivax* and *P. falciparum*, the method of approach being the same as previously described. Volunteers who received "build-up" doses of SN 6,911 of 0.2 gm. twice daily for 4 days before exposure to infection and then had 0.1 or 0.2 gm. daily during the period of exposure and for 23 days after the last infective bite had smears completely parasite free (except one patient who had one parasite on 1 day only), and they had no attacks of malaria. Following discontinuance of suppressive medication, all volunteers infected with *P. vivax* developed acute attacks (average 27 days), but none of those infected with *P. falciparum* developed malaria within 92 days after discontinuance of the drug. In the latter group, cure was demonstrated by failure to

produce malaria in recipients who were given 200 cc. of blood from the test subjects. No immunity was demonstrated since subsequently it was possible to induce malaria in the same subjects with the same strain of *falciparum* parasites. Subinoculation of blood from subjects treated with SN 6,911, on the eighth and ninth days after reinfection with *P. falciparum* produced malaria in the recipients. These studies therefore showed that SN 6,911 was curative in *falciparum* infections through its effect on the parasites after they reached the peripheral blood.

In an experiment of simulated field type, volunteers were heavily exposed to infection for 58 days while suppressive doses of 0.1 gm. SN 6,911 were given daily; this dosage was continued for 28 days after the last infective bite. In addition, the men were subjected to extreme exercise, cold, and adrenalin injections. During the period of exposure and continued suppression, no parasitemia or clinical malaria occurred. After the drug was stopped, malaria developed in all volunteers infected with *P. vivax* and in none of those infected with *P. falciparum*. Control studies with similar doses of quinacrine gave identical results.

Toxicity

No toxic manifestations related to SN 6,911 were reported from these studies in which more than 200 patients were given 5.2 gm. of drug during 7 days' treatment for acute attacks of *vivax* malaria. There were no toxic signs or symptoms in subjects who received 0.1 or 0.2 gm. daily for suppression for several weeks or months nor were any noted in subjects who received 0.4 gm. daily for 20 or more days. No skin discoloration was observed.

Convulsions occurred during the administration of SN 6,911 in three patients with general paresis and malaria. Acute confusional psychosis was observed in two additional patients with plasma concentrations over 400 μg. per liter. One patient who had 1.5 gm. of SN 6,911 intravenously after a preliminary full therapeutic course of quinacrine developed a convulsion. The drug was given in a 2.5 percent saline solution, injected at the rate of 1 cc. per minute. Plasma levels in the order of 1,000 μg. per liter at the end of the injection and levels above 200 μg. 24 hours later were observed in other patients who received similar amounts of SN 6,911 intravenously.

Experience with SN 6,911 was not sufficiently prolonged or extensive to permit the accumulation of data with regard to more chronic toxic manifestations of the nature reported from prolonged quinacrine administration. However, it is of interest that stimulation of the central nervous system was demonstrated in subjects with high plasma levels of SN 6,911.

Summary

SN 6,911 was found to be as effective as quinacrine, except for the briefer interval between relapses after cessation of treatment, but was in no way superior to quinacrine, except that it did not discolor the skin. It might have proved a useful substitute had there been a serious breakdown in the

use of quinacrine because of alleged or proved toxicity. These studies stimulated further syntheses and alterations of various 4-amino acid compounds which ultimately resulted in a drug that was, in fact, superior to quinacrine. This was SN 7,618, or Chloroquine Diphosphate.

Chloroquine Diphosphate (SN 7,618)[57]

An intensive 2-year study was made of this drug in man and in experimental animals. Its pharmacology was studied in fairly extensive experiments with mice, rats, dogs, monkeys, and man. Extensive studies were made on its prophylactic activity against domestic strains and Southwest Pacific strains of *vivax* malaria, on its curative activity against sporozoite-induced infections when administered alone and in combination with other compounds, and on its suppressive activity. Large-scale investigations of its use in terminating the acute attack and for suppression were carried out in military installations. Most of these studies were made in comparison with quinine.

General properties

Absorption of SN 7,618 from the gastrointestinal tract is complete or nearly complete, and somewhat more rapid than absorption of quinacrine. Like quinacrine, SN 7,618 is metabolized in the body. Only 10 to 20 percent is excreted unchanged in the urine; this fraction can be increased by acidification of the urine, decreased by alkalinization. On any given dosage schedule there are substantially higher concentrations of SN 7,618 in the plasma, since there is less localization in the tissues than there is with quinacrine. The pattern of distribution is in general similar. SN 7,618 is concentrated in nucleated cells (also in leukocytes); the liver, spleen, kidneys, and lungs contain from 200 to 500 times the amount in the plasma, while the brain and spinal cord contain no more than 10 to 25 times the plasma concentration.

The marked localization of this drug in the organs, together with the slow rate of excretion and degradation, necessitate a priming dose if the desired concentration in the plasma is to be rapidly reached and maintained. As with quinacrine, these factors result in slow disappearance of the drug from the body when it is discontinued; its concentration in the body fluids generally falls about 60 percent per week when administration stops.

Antimalarial activity

SN 7,618 proved more active than quinacrine in all of the avian malarias in which it was tested. In *Plasmodium cathemerium* both in the canary and in the duck it is 3.5 times as active as quinacrine, 5 to 13 times as active against *Plasmodium gallinaceum* and 2.5 times as active in *Plasmodium lophurae* in the duck. Like quinacrine, it does not produce permanent cures in any of these infections, nor is either drug prophylactic in sporozoite-

[57] Formula: 7-Chloro-4-(4-diethylamino-1-methylbutylamino) quinoline diphosphate.

induced *cathemerium* malaria in the canary or *gallinaceum* malaria in the chick.

SN 7,618 is highly active against erythrocytic forms of *P. vivax* and *P. falciparum*. It does not prevent relapses in *vivax* malaria even in doses many times those required to terminate an acute attack, nor will it prevent the establishment of a *vivax* infection when administered as a prophylactic. It is highly effective as a suppressive agent and in the termination of the acute attack, significantly lengthening the interval between treatment and relapse beyond that observed with quinacrine or quinine. In *falciparum* malaria it has been shown to suppress the acute attack and to effect complete cure of the infection. Studies of the antimalarial activity of SN 7,618 against well-standardized strains of *P. vivax* and *P. falciparum* have shown it to be approximately three times that of quinacrine. In well-tolerated therapeutic doses a great majority of patients will be afebrile within 24 hours and the remainder within 48 hours. Thick smears for parasites will generally be negative at 48 to 72 hours.

Mean plasma levels in the range of 10 μg. per liter have been shown to be effective in treating attacks of induced *vivax* malaria. Initial oral doses of as little as 100 mg. followed by daily doses of 85 mg. for 4 days produce plasma levels above the therapeutic range and result in termination of the attack. The therapeutic level for terminating attacks due to *P. falciparum* are in the range of 20 μg. per liter and such levels and clinical effects have been produced with initial doses of as little as 150 to 300 mg. followed by daily doses of approximately the same amount for 4 to 6 days. It is evident from these observations that the antimalarial activity of SN 7,618 is significantly greater than quinacrine both on the basis of oral dosage and plasma drug concentration.

Clinical testing

SN 7,618 has been given to more than 1,000 patients with acute attacks of *vivax* malaria of domestic, Pacific, and Mediterranean origin. The clinical testing of this drug in *vivax* malaria of war origin was carried out principally at Harmon and Moore General Hospitals, designated as specialized treatment centers in the United States for the study of tropical diseases. Other studies in the U.S. Army with SN 7,618 were carried out overseas. In addition, clinical and toxicologic investigations were conducted at various naval, Federal, and civilian installations in this country and abroad as well as by investigators of Allied Nations.

The observations on the use of SN 7,618 in the treatment of *vivax* malaria reported from Moore General Hospital,[58] summarized in the following paragraphs, are representative of other reported studies.

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[58] Most, H., London, I. M., Kane, C. A., Lavietes, P. H., Schroeder, E. F., and Hayman, J. M., Jr.: Chloroquine for Treatment of Acute Attacks of Vivax Malaria. J.A.M.A. 131: 963-967, 20 July 1946.

STUDY AT A SPECIALTY CENTER

Material and methods.—The patients were military personnel who had acquired *vivax* infections in the Pacific area or Mediterranean theater. All phases of the disease, first attacks as well as early and late relapses, were represented by significant numbers of men. Approximately 50 to 75 patients were included in each of the five treatment plans.

All patients with an acute clinical attack were admitted to two special-study wards for observation and therapy with SN 7,618. No patient was treated unless his blood smear was positive for malaria parasites and his temperature over 100° F. Cases were selected only with respect to the geographic origin and age of the disease, to ensure adequate representation on each treatment schedule.

All treatment was begun on the morning following the onset of the current attack. Parasite counts were done twice daily and continued until negative for 3 consecutive days. The plasma levels of SN 7,618 were ascertained frequently during and after treatment to determine the pattern of accumulation, stabilization, and disappearance of the drug from the plasma. Temperatures were taken every 4 hours during treatment and every 15 minutes during a paroxysm. The clinical response was followed during daily rounds. All signs and symptoms possibly related to malaria or to treatment with SN 7,618 were recorded. In addition, clinical and laboratory observations were directed specifically to recognizing possible toxic manifestations. All drugs were administered by a medical officer.

Following completion of treatment and study on the wards, the patients were transferred to a convalescent area on the hospital grounds for observation until relapse or for 120 days from the last day of treatment.

During this interval smears were examined twice weekly. In the event of parasitemia the temperature was recorded three times daily and smears made every day. A temperature rise of over 100° F. by mouth associated with a positive smear was considered a relapse, and the patient was readmitted to a ward for further observation and treatment. Approximately 80 percent of the relapsed cases were direct admissions from the convalescent area following paroxysms with temperatures of from 103° to 105° F. The other 20 percent were admitted as a result of temperature observations made during interval parasitemia. Of the latter group at least one-half developed paroxysms shortly after admission to the ward. No patient was treated without coincident fever and parasitemia.

Treatment plans.—Protocols for treatment schedules were furnished by the Office of the Surgeon General. Representative treatment schedules which have been found most satisfactory are presented in table 74. (Tablets of 0.1 gm. and 0.3 gm. of SN 7,618 [59] were available and were used singly or in combination to supply the proper individual dose.)

Other treatment plans consisting of the administration of a total of 0.8 gm. during 7 days and 1.5 gm. during 3 days were also studied.

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[59] The dosage, wherever it appears in this chapter, is in terms of base. This drug was not commercially available at the time these studies were made, and the tablets were specially prepared.—H.M.

TABLE 74.—*Representative treatment schedules for chloroquine*

Schedule	Hour	Dosage (grams)
Plan A:		
1st day	8 a.m.	0.4
	12 m.	0.3
	5 p.m.	0.3
Total		1.0
Plan B:[1]		
1st day	8 a.m.	0.3
	12 m.	0.3
2d day	8 a.m.	0.3
3d day	8 a.m.	0.3
4th day	8 a.m.	0.3
Total		1.5
Plan C:		
1st day	8 a.m.	0.4
	12 m.	0.2
	5 p.m.	0.2
2d day	8 a.m.	0.2
3d day	8 a.m.	0.2
4th day	8 a.m.	0.2
5th day	8 a.m.	0.2
6th day	8 a.m.	0.2
7th day	8 a.m.	0.2
Total		2.0

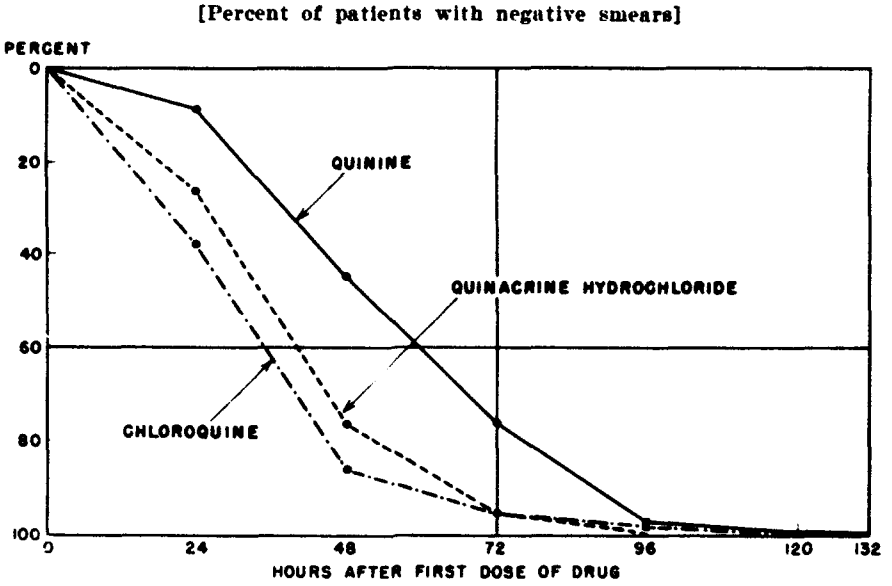
[1] This schedule advocated for routine use.

Results.—These results are as follows:

1. ***Control of parasitemia.***—The rate of disappearance of parasites from the peripheral blood during the administration of SN 7,618 in comparison with quinine and quinacrine are shown in chart 31. It may be seen that the peripheral blood becomes free of parasites more rapidly with SN 7,618 (plans A, B, and C) than with either of the other drugs, the difference being more marked between SN 7,618 and quinine than between SN 7,618 and quinacrine. The superiority of SN 7,618 was manifest in *vivax* malaria of Mediterranean or Pacific origin in first attacks as well as in relapses occurring at any stage of the disease.

2. ***Control of fever.***—In a total of 244 attacks treated with SN 7,618 according to plans A, B, and C, only 5 patients or 2.1 percent had fever (temperature of 100° F. or more) the day after treatment was begun or subsequently. By contrast, treatment with quinine in 184 attacks and with quinacrine in 391 attacks was associated with fever on the second day or later in

CHART 31.—*Comparative rate of disappearance of parasites from peripheral blood during treatment of* vivax *malaria with quinine (172 attacks), quinacrine hydrochloride (397 attacks), and chloroquine (293 attacks)*

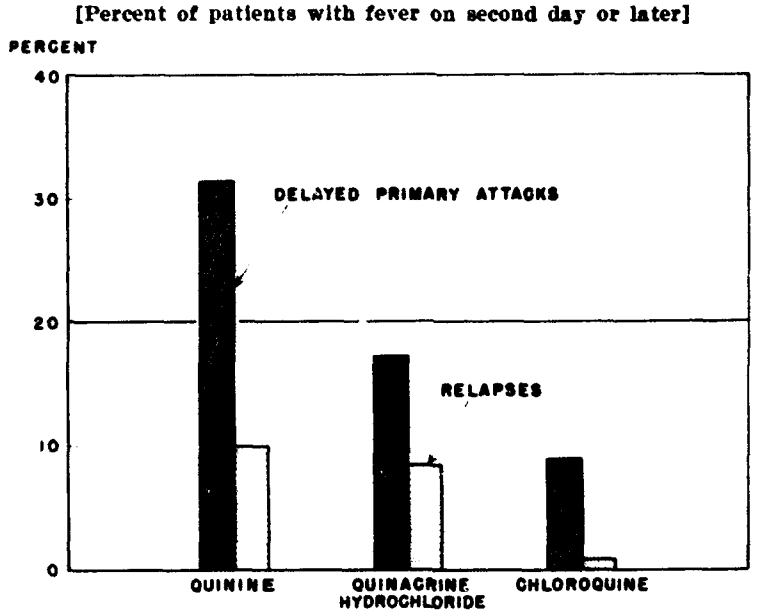


8.7 and 8.0 percent, respectively, of patients treated. The superiority of SN 7,618 in this respect is manifest in infections of both Mediterranean and Pacific origin, regardless of the initial parasite density, and in Pacific infections regardless of whether the attack is the very first or a relapse at any stage of the disease. In delayed primary attacks the proportion of patients who have fever on the second day after treatment with SN 7,618 is begun is higher than in patients treated in relapse. This is also true even to a greater extent for delayed primary attacks treated with quinine or quinacrine, shown in chart 32.

3. ***Control of symptoms.***—It is difficult to evaluate comparative effects of quinine, quinacrine, and SN 7,618 in controlling symptoms which are usually present for a few days in a treated attack of malaria. However, clinical impressions based on treatment of more than 1,000 acute attacks of *vivax* malaria and supported by a more detailed statistical analysis, indicate that SN 7,618 is at least as good as quinine or quinacrine in the control of all symptoms, and is superior to one or the other in the control of some symptoms.

Headache and backache are relieved more rapidly with SN 7,618 or quinine than with quinacrine. Quinine is more effective than quinacrine in the control of generalized aching, but is not significantly better than SN 7,618. Weakness, dizziness, and lightheadedness disappear more rapidly with SN 7,618 or quinacrine than with quinine. Nausea persists longer in patients treated with quinine than in those treated with SN 7,618 or Atabrine. The effect of each of these drugs on the duration of vomiting, abdominal pain, and abdominal tenderness is essentially the same.

CHART 32.—*Comparative efficiency of quinine, quinacrine hydrochloride, and chloroquine in controlling fever during treatment of delayed primary attacks of relapses of* vivax *malaria*



4. ***Effect on interval to relapse.***—Quinine, quinacrine, and SN 7,618 do not materially influence the ultimate relapse rate following treatment of the acute attack. Apparently the ultimate relapse rate in large groups is not affected by the age of the disease, the number of previous attacks, total amount of drug, or duration of treatment. More than 500 patients treated for acute attacks of *vivax* malaria of Pacific and Mediterranean origin were followed to relapse, or for a minimum of 120 days. The relapse rates following treatment with quinine, quinacrine, or SN 7,618 were from 75 to 85 percent for Pacific infections and approximately 35 percent for Mediterranean infections. The cumulative relapse rates following treatment of acute attacks of *vivax* malaria of Pacific origin are shown in chart 33. At 120 days, 85, 80, and 70 percent of patients treated with quinine, quinacrine, and SN 7,618, respectively, had relapses.

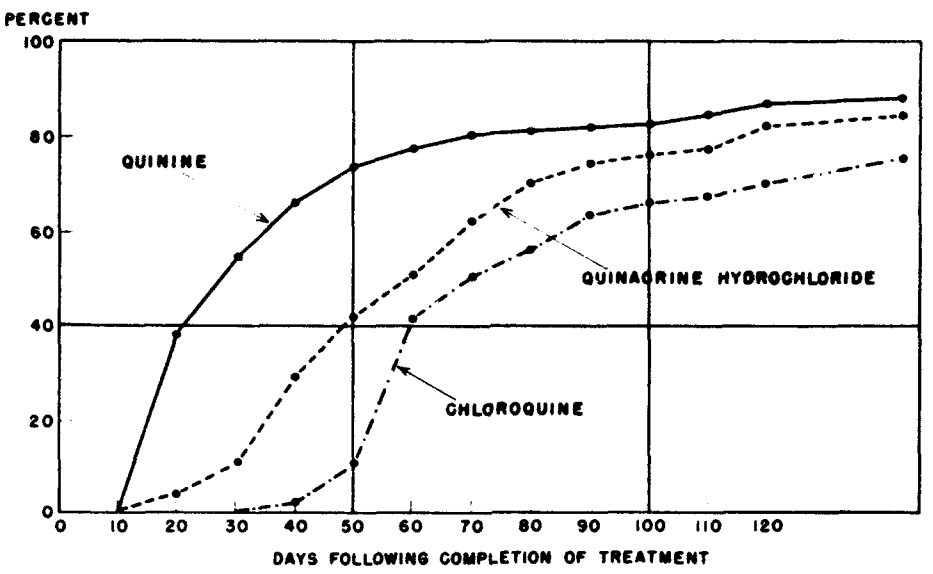
The interval to relapse, however, and the distribution of the relapses that occurred during the first 2 months after treatment are strikingly different for the three drugs. These differences are presented in chart 34.

During the first month after treatment, 54 percent of the patients treated with quinine relapsed, 9 percent relapsed after quinacrine, and none relapsed after SN 7,618. At 40 days, relapses following SN 7,618 begin to occur, but these represent less than 1 percent of treated patients, whereas 67 and 28 percent relapsed at 40 days after treatment with quinine and quinacrine, respectively. At 50 days, 72, 40, and 11 percent of the patients relapsed after quinine, quinacrine, and SN 7,618, respectively.

In terms of the total number of relapses that occur within 120 days, the percentages of patients who relapsed within 50 days were 85, 50, and 16 percent, respectively, for quinine, quinacrine, and SN 7,618. Thus, of the total relapses that occur within 120 days, more than three-fourths of them will take place in the first 50 days after quinine,

while during the same time after quinacrine only one-half, and after SN 7,618 only one-sixth will occur. The median interval to relapse following treatment with quinine is 24 days, with quinacrine, 50 days, and with SN 7,618, 61 days.

CHART 33.—*Cumulative rates of relapses during a minimum of 120 days following treatment of acute attacks of* vivax *malaria with quinine (76 patients), quinacrine hydrochloride (118 patients), and chloroquine (156 patients)*



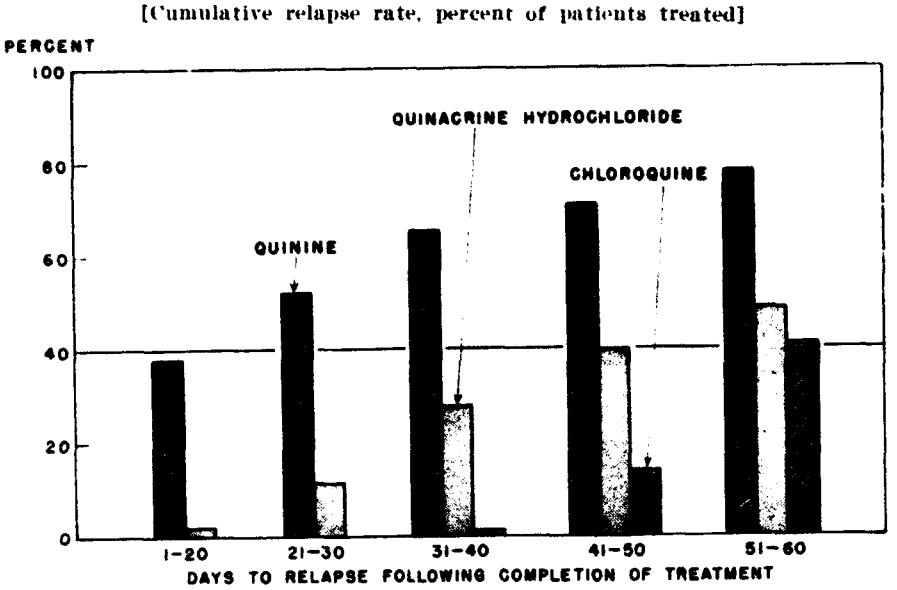
Since none of these drugs produces a complete cure of malaria, the drug of choice on the basis of interval to relapse is the one that gives the longest mean interval, the greatest median interval for a large group of patients, and the smallest number of short-term relapses. The data presented show that the interval to relapse after treatment with SN 7,618 will be on the average at least 5 weeks longer than after quinine and about 2 weeks longer than after quinacrine. Only a negligible number of patients treated with SN 7,618 will relapse during the first 50 days after treatment. Accordingly, SN 7,618 not only controls symptoms, fever, and parasitemia promptly but, in addition, confers freedom from another attack for a period of approximately 2 months.

Plasma levels.—Blood was drawn at such times as to determine the rate of accumulation, stabilization, and disappearance of SN 7,618 from the plasma during and after treatment with various dosage regimens. The values obtained during and after treatment on schedules A, B, and C are presented in chart 35.

The minimal plasma concentration of SN 7,618 that is effective in terminating an acute attack has been shown to be in the range of 10 μg. per liter. The levels observed during and after treatment on plans A, B, or C are well above this range.

No correlation has been found between variations observed in levels obtained in single individuals receiving the same amount of drug and their interval to relapse or to the first parasitemia after completion of treatment.

CHART 34.—*Comparison of distribution of relapses occurring during the first 60 days after treatment of acute attacks of* vivax *malaria of Pacific origin with quinine, quinacrine hydrochloride, and chloroquine*



Summary.—The data presented in the study on the relative efficiency of quinine, quinacrine, and SN 7,618 are summarized and presented for reference in table 75.

TABLE 75.—*Relative efficiency of quinine, quinacrine hydrochloride, and chloroquine in treatment of acute attacks of* vivax *malaria*

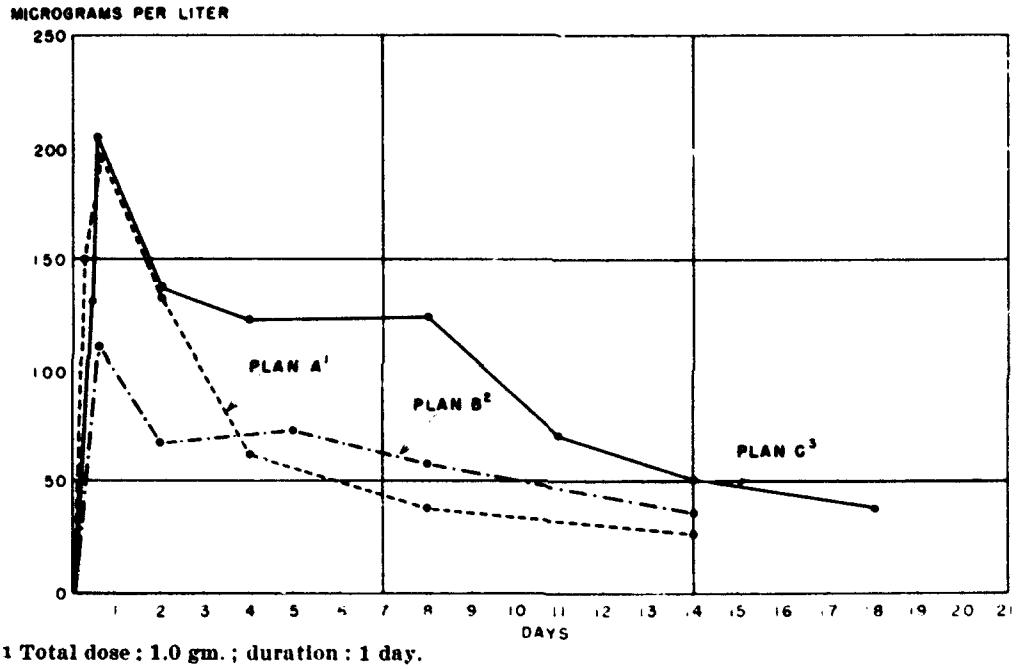
Efficiency factors	Quinine	Quinacrine hydrochloride	Chloroquine (SN 7,618)
Total amount of drug.....grams..	28. 35	2. 8	[1] 1. 0, 1. 5, 2. 0
Duration of treatment.....days..	14	7	[1] 1, 4, 7
Rate of parasite clearance.....	+	+ + +	+ + + +
Control of fever:			
Delayed primary attacks [2].....	+	+ +	+ + +
Relapses [3].....	+ +	+ +	+ + + +
Interval to relapse:			
Median.....days..	24	50	61
Relapses:			
First 50 days.....percent..	85	50	16
Total, 120 days.....do....	90	82	75
Control of symptoms.....	+ +	+ + +	+ + + +
Toxicity.....	[4] + + +	[5] +	[6] +

[1] Plans A, B, and C. See table 74.
[2] Infections of Pacific origin.
[3] Infections of Mediterranean or of Pacific origin.
[4] Cinchonism.
[5] Eczematoid reactions in patients sensitive to quinacrine hydrochloride.
[6] Slight, transitory pruritus; rare erythema or urticaria.

From this study it was concluded that SN 7,618 is a highly effective, safe antimalarial drug which is superior to quinine and quinacrine in the treatment of acute attacks of *vivax* malaria. Routine treatment was recommended as follows:

One tablet (0.3 gm.) of SN 7,618 is administered when the diagnosis of *vivax* malaria is established by a positive blood smear. This amount of drug (0.3 gm.) is repeated 4 hours after the first dose. One tablet (0.3 gm.) is then given on each of the following three mornings. The total dose is 5 tablets, totaling 1.5 gm. of SN 7,618 administered during 4 days.

CHART 35.—*Average plasma levels of chloroquine (176 patients) during and after treatment under plans A, B, and C*



1 Total dose: 1.0 gm.; duration: 1 day.
2 Total dose: 1.5 gm.; duration: 4 days.
3 Total dose: 2.0 gm.; duration: 7 days.

NOTE.—In all schedules, the mean plasma levels during treatment are from 7 to 20 times above the required therapeutic level. Note also the persistence of the drug long after termination of treatment.

OTHER STUDIES OF *VIVAX* INFECTIONS

Treatment plans with SN 7,618 in which total doses of 1.0 gm. in 1 day, 0.8 gm. in 6 days, 2.0 gm. in 6 days, and 1.2 gm. in 3 days were studied at Harmon General Hospital. The results reported from a total of 235 attacks treated on the above schedules were essentially the same as those reported from the Moore General Hospital. Treatment of primary attacks of Pacific origin or relapses of Pacific or Mediterranean *vivax* malaria with SN 7,618 resulted in prompt control of symptoms. Parasitemia and fever disappeared more promptly than with quinacrine, and the interval to relapse was greater

ıan with the latter except in the patients who had a total of only 0.8 gm. SN 7,618 during 6 days. It was felt that SN 7,618 was superior to other ıtimalarial agents previously studied at that installation (quinine, quinaine, and SN 6,911).

A single dose of 1.0 gm. SN 7,618 was administered to each of 50 patients ith acute attacks of *vivax* malaria at a U.S. naval installation. There was rompt subsidence of fever, and parasites disappeared in all cases within 36 ours. The interval to relapse from this single-dose schedule was longer ıan that following the standard quinacrine course. At another naval installtion, more than 100 patients were treated with SN 7,618 for acute attacks of *vax* malaria of Pacific origin. The majority received 1.0 gm. within a eriod of 16 to 24 hours. Control of symptoms and fever was more prompt ıan was observed in patients treated with quinacrine, and parasites disapeared from the blood in most cases within 48 hours. Short-term relapses. ıat is, less than 40 days, did not occur after treatment with SN 7,618, in ontrast to a significant number of relapses in less than 40 days after treatent with quinacrine.

SN 7,618 was used clinically to terminate acute attacks of *vivax* malaria various oversea areas. In India, 26 American military patients with acute *vax* infections were treated with 0.9 gm. during the first 24 hours followed a single dose of 0.3 gm. on each of the 2 successive days (total 1.5 gm. in days). The average duration of fever was 24.1 hours and parasitemia 1.5 ays. In Peru, more than 300 natives were treated for acute attacks of *vivax*, *lciparum*, and mixed malaria with relatively small doses of SN 7,618 (0.75 n. on the first day and 0.25 gm. on the second day; total 1.0 gm. in 2 days). ı 70 cases carefully studied, blood smears were positive in only 17 and 5 at and 48 hours, respectively, after the initiation of therapy. The clinical sponse to treatment was considered good in the majority of patients. It was oted the *falciparum* infections responded more slowly than those due to . *vivax*.

STUDIES OF *FALCIPARUM* INFECTIONS

SN 7,618 did not have any extensive clinical trial in the treatment of *lciparum* infections, particularly the fulminating variety with cerebral volvement. Preliminary studies in this country with injections of domestic rains of *P. falciparum* indicated that plasma concentrations of 20 μg. of ug per liter maintained for 4 to 6 days resulted in the control of fever and ırasitemia without recurrence of symptoms or signs of infection for 14 days more. Such relatively low plasma levels are easily obtained with initial oses of 200 mg. and maintained with daily doses of 100 mg. In actual prace, the oral dosage schedules of 0.6 to 1.0 gm. during the first 24 hours folwed by daily doses of 0.2 to 0.3 gm. result in plasma levels of 5 to 10 times at required to terminate *falciparum* activity. It is probable therefore that N 7,618 would prove effective in terminating most infections with *P. lciparum*.

At the 20th General Hospital in the India-Burma theater, 10 Chinese soldiers with acute *falciparum* malaria were treated with 1.5 gm. of SN 7,618 during 3 days. Clinical response was satisfactory in all patients. The average duration of fever (102° to 105° F. at onset) was 34 hours after the first dose (range 8 to 64 hours), and blood smears became negative within 3 days. In another report from the same hospital, similar results were recorded in eight American soldiers with acute *falciparum* malaria treated with SN 7,618 (total 1.5 gm. during 3 days). The average duration of fever (102.4° to 104.8° F. at onset) was 28.4 hours after the first dose, and blood smears were free of parasites within 1 to 3 days.

In the Peru study of more than 300 acute attacks of malaria (many *P. falciparum* or mixed *vivax-falciparum*) treated with a total of 1.0 gm. of SN 7,618 during 2 days, 17 infections with *P. falciparum* and 7 mixed cases were closely followed; the response to treatment was considered rapid or good. There were no treatment failures. Fever and parasitemia were quickly controlled. In general, the rapidity of disappearance of parasites and the clinical response to treatment varied with the severity of the infection. It should be borne in mind that the total duration of treatment and total doses of drug employed were no optimum and that the satisfactory response was observed in highly immune natives who are not comparable with nonimmune American troops.

Unfortunately, no parenteral SN 7,618 was available, and no opportunity was afforded for comparing the relative efficiency of SN 7,618 and parenteral quinine or quinacrine in the treatment of fulminating *falciparum* infections complicated by severe vomiting or involvement of the central nervous system.

STUDIES OF SUPPRESSION

The suppressive efficacy of SN 7,618 and the mode of its action against *vivax* and *falciparum* infections were investigated in Australia in the manner of similar studies of quinine, quinacrine, and SN 6,911.[60] New Guinea strains of *P. vivax* and *P. falciparum* were employed. The "build-up" doses of SN 7,618 were 0.2 gm. twice daily for 4 days. Subsequently, the daily dosage was 0.1 gm. continued for 23 days after the last exposure to infective mosquitoes. None of the volunteers infected with *P. vivax* or *P. falciparum* developed clinical malaria or microscopically detectable parasitemia during the period of suppression. However, subinoculation of 200 cc. of blood to other volunteers 9 or 10 days after infection produced malaria in the recipients. This proved that the test subjects were infected and demonstrated that the action of SN 7,618 was not prophylactic and that its suppressive action against the parasites was exerted after their appearance in the blood. Following discontinuance of medication, all volunteers infected with *P. vivax* developed malaria within 40 to 60 days, but no *falciparum* malaria developed during a

[60] See footnote 12, p. 529.

period of 81 days in the men infected with *P. falciparum*. SN 7,618 was thus shown to be equally as effective as quinacrine or SN 6,911 in suppressing both *vivax* and *falciparum* infections and in curing the latter.

Anticipating the practical application of SN 7,618 as a suppressive agent, one must consider the persistence of this drug in the body and the fact that relatively low plasma levels (10 μg. per liter) have pronounced antimalarial activity. It was shown that the administration of 0.3 gm. of SN 7,618 in single doses once a week resulted in the maintenance of mean levels above 10 μg. per liter in the majority of more than 50 subjects who remained on this suppressive schedule for 4 to 8 weeks.

Suppressive schedules of single weekly doses of SN 7,618 were studied, in this country, in patients with recurrent *vivax* malaria of Pacific origin. Ninety-four men who previously were having frequent relapses were placed on 0.3 gm. weekly for approximately 3 months. During the period of suppression, only one man had a positive blood smear on one occasion. During the last 10 days of suppression, 75 men were placed on an extremely rugged test of physical endurance, consisting of daily hikes of 5 to 15 miles over very rough terrain, forced marches, and rifle drill. In this period, six men developed transient parasitemia. No clinical attacks occurred during suppression, including the period of exercise. It was calculated on the basis of the number of attacks these men had had in 3 months prior to suppression that at least 75 relapses should have occurred if no suppressive therapy had been taken. It was thus shown that SN 7,618 given once a week was completely effective in suppressing clinical malaria in a group with a high index of relapse and parasitemia (positive smears in 84 percent in the 5-week period prior to suppression).

At Moore General Hospital, more than 100 patients who had had an attack of *vivax* malaria within the previous 3 months were placed on 0.3 gm. SN 7,618 once a week for 8 to 16 weeks. More than half of these patients had tuberculosis. During the period of suppression, no parasitemia and no clinical malaria occurred. The patients, especially those with tuberculosis, were reluctant to discontinue their weekly dose of SN 7,618 because they felt reassured that they would not have malaria while they were taking the drug.

In a series of more than 200 men treated with 1.0 gm. of SN 7,618 in 1 day for acute attacks of *vivax* malaria of Pacific origin, the shortest interval to relapse was 33 days. It was therefore believed that successful suppression could be accomplished by the administration of 1.0 gm. in 1 day at monthly intervals. Accordingly, 35 men recently treated for an acute attack with 1.0 gm. of SN 7,618 in 1 day were advised to take 1.0 gm. within 1 day every 4 to 6 weeks. They were observed from 60 to 162 days while on this schedule of self-medication. In this period, the expected number of relapses was calculated to be 24, but only 8 occurred. It is possible that, if medication had been supervised and administered regularly once a month rather than at irreg-

ular intervals up to 6 weeks, more effective or complete suppression might have been produced. Thus, SN 7,618 is not only effective as a suppressive with weekly doses of 0.3 gm. but it is possible that satisfactory suppression may result from larger doses at greater intervals.

Studies on suppression with SN 7,618 were made in various areas overseas: In Peru, in more than 1,200 adults and children (natives); in India, in school children, in coolies, and in colored troops; and in the Philippines, in American soldiers during, unfortunately, a time when there was practically no transmission of malaria. Military deactivation of units prevented completion of the last investigation as previously planned. In all these studies, the results were good, but such observations in natives, or in American troops during periods of nontransmission, offered no conclusive evidence that complete suppression under combat conditions in highly malarious areas would result from the administration to troops of a weekly dose of 0.3 gm. of SN 7,618.

The experiments in Australia, the observations on the control of parasitemia overseas, and the suppression of relapses in this country indicate, however, that SN 7,618 in weekly suppressive doses should prove effective under combat conditions. The apparent advantage of SN 7,618 as a suppressive agent lies in the ease of administering it in the form of one tablet once a week, the absence of the yellowish discoloration of the skin resulting from the prolonged use of quinacrine, and its tolerability.

Toxicity

Extensive studies of the acute and chronic toxicity of SN 7,618 were conducted in animals prior to its clinical application in man. Observations were made on the tolerability and toxicity of varying amounts of drug administered to human volunteers, often for prolonged periods. Finally, data collected on possible toxic signs or symptoms during the administration of therapeutic or suppressive amounts of SN 7,618 in several thousand individuals furnished the background for the following statement approved by the Board of Coordination of Malarial Studies:

There is little difference in the toxicity of SN 7,618 and that of quinacrine in experimental animals. The acute toxicity of both drugs given orally is about the same in the rat and monkey. The acute toxicity of intravenous SN 7,618 is greater than that of quinacrine in the dog. Short-term chronic toxicity tests in the mouse show the two drugs are about equally toxic. In such tests carried out in the rat and the monkey for periods not exceeding 30 days, SN 7,618 is slightly more toxic than quinacrine. In longer term studies with the rat and monkey extending up to 120 days, the drugs are about equally toxic or, if anything, SN 7,618 is slightly less toxic than quinacrine.

In man, the symptoms that have been observed following doses of SN 7,618 adequate for treatment of the acute attack include mild and transient headache, visual disturbances, pruritus, and gastrointestinal complaints. In chronic toxicity studies in man using a dose (0.5 gm. weekly) in excess of that necessary for adequate suppression, no serious symptoms and no impairment of health have been observed in 31 subjects over a period of 11 months of consecutive drug administration. In studying the record

of 2,655 individuals who have received SN 7,618, every symptom that has been observed has been recorded in an effort to bring out even minimal toxic manifestations. In a small number of instances, usually with dosages higher than necessary for either treatment or suppression, individual subjects have refused to continue drug administration because of unpleasant symptoms; none of these manifestations has been constitutionally serious and all have been readily reversible. Unlike quinacrine, SN 7,618 does not discolor the skin.

Statements on toxicity in various reports concerned with the therapeutic or suppressive use of SN 7,618 will be briefly cited.

In a treatment study[61] in which 365 patients with acute attacks of *vivax* malaria were given total doses of 0.8 to 2.0 gm. of SN 7,618 during a period of 1 to 7 days, no major toxic manifestations were encountered clinically or in numerous laboratory investigations. It was not necessary to interrupt or discontinue treatment in a single case. Occasionally, there was mild nausea if the drug was taken in the fasting state. No visual disturbances were noted. Particular effort was made to detect cutaneous symptoms or signs that might be attributed to SN 7,618, and special questioning elicited information that would rarely have been volunteered. Of the 284 patients treated with SN 7,618, 56 complained of pruritus during the course of drug administration. The pruritus was occasionally generalized but more often localized, particularly to the palms and soles, and in the great majority it was transitory and very mild. Of the 56 patients who developed pruritus, 50 had no coincident skin eruptions. Seven patients, or only 2.4 percent of the total number treated, developed erythema, urticaria, or a mild papular eruption. No similar emphasis was placed on skin symptoms in patients treated with quinine or quinacrine and it is likely that the reported incidence in association with SN 7,618 therapy is disproportionately high. In this study, the administration of SN 7,618 to patients with eczematoid dermatitis or the eczematoid-lichen-planus complex due to quinacrine did not result in exacerbation of the underlying skin condition in any case.

In another series of 236 patients treated with similar total doses of SN 7,618 the incidence of pruritus was 7 percent but urticaria or rash occurred only in 3 cases. Visual disturbances were not encountered. Gastrointestinal symptoms were negligible.

Visual disturbances, that is, blurred vision and difficulty in shifting fixation from near to distant objects, have been described in volunteers on daily doses of 0.5 gm. SN 7,618 and in patients treated for acute attacks of *vivax* malaria with 3.2 gm. These symptoms are undoubtedly of importance in evaluating the toxicity of SN 7,618 since they originate in the central nervous system. It must be pointed out, however, that symptoms or signs have not occurred in almost 1,000 patients treated with total doses of less than 2.0 gm. or with suppressive doses of not more than 0.3 to 0.5 gm. per week. The amounts of SN 7,618 reported to have produced visual disturbances are in the order of 10 times that required for adequate suppression and 2 to 4 times the required dose for termination of an acute attack.

In the field studies of suppression that have been cited, based on several thousand subjects, no striking toxicity is noted, and the incidence of gastrointestinal or other symptoms requiring the discontinuance of the drug is remarkably low. Detailed investigations of the effects of SN 7,618 suppression on various organ functions were carried out at Randolph Field, San Antonio, Tex. Doses of 0.5 gm. weekly and twice weekly

[61] See footnote 58, p. 563.

were given for 4 weeks. No significant effects on physical fitness, on psychological performance at ground level and at 18,000 feet, on vision (as indicated by scotopic vision, visual fields, or near-point accommodation), on auditory acuity, on heart (as indicated by electrocardiograms), or on ability to retain balance while blindfolded, were observed.

Observations on the prolonged administration of SN 7,618 were made in conscientious objectors. Forty men given 0.3 gm. daily for 77 days and then 0.5 gm. weekly for 12 weeks showed no serious toxic reactions. Headache and difficulty in quickly fixing on distant objects occurred in this group on very large doses. Visual symptoms persisted in only 2 men of 31 who remained on the drug for 9 months. Bleaching of the hair at the roots was observed in five blonde subjects while they were receiving 0.3 gm. of SN 7,618 daily. The color of the hair returned to normal when the drug was discontinued. One patient given SN 7,618, 0.5 gm. weekly, for 8 months developed an eruption resembling lichen planus which persisted during the subsequent administration of the drug and began to subside 2 weeks after its discontinuance.

The last observation is of extreme importance in that it suggests the possibility that the prolonged administration of SN 7,618 in large doses may result in the dermatitis complex (eczematoid dermatitis and/or lichen planus) described with quinacrine suppression. In this connection it is of interest that of 30 patients with atypical lichen planus who were placed on suppression doses of SN 7,618 in the India-Burma theater (0.3 gm. weekly), one suffered an actual flareup of the dermatitis described as a mild acute eczematoid reaction which came on after one dose and disappeared within 2 days. It must be remembered that patients with eczematoid dermatitis may react to many drugs. At Moore General Hospital more than 50 patients with atypical lichen planus and a like number with eczematoid skin conditions were given SN 7,618 for termination of acute attacks of malaria. There was no exacerbation in the skin disease in these cases, and in a group of patients with lichen planus who continued on suppressive therapy of 0.3 gm. weekly up to 3 months, no change was noted in the lichenoid lesions other than continued regression.

The toxic manifestations of SN 7,618 may be summarized briefly. Little to no toxicity was encountered with therapeutic (1.0 to 2.0 gm.) or suppressive (0.3 gm. weekly) doses of SN 7,618. Minor toxic symptoms consisted of occasional gastrointestinal complaints and pruritus in a small number of subjects. Following large doses for therapy or suppression, visual disturbances occurred, and in one case atypical lichen planus developed after suppressive medication for 8 months (0.5 gm. weekly). In general, it was felt by most observers that SN 7,618 in recommended doses was a safe drug.

Summary

Clinical experience with SN 7,618 proved this drug to be a highly effective antimalarial agent, superior to quinacrine, quinine, and SN 6,911. It excels quinacrine and quinine in more prompt control of fever, symptoms, and parasitemia, in a shorter course of treatment, in a longer interval to relapse, in the abolition of short-term relapses, and in freedom from major toxic reactions. Given in single weekly doses, SN 7,618 is able to provide effective suppression against *vivax* and *falciparum* infections and to cure the latter. SN 7,618 does not discolor the skin. Unfortunately, no assay of its value in fulminating *falciparum* infections was possible. Experience has shown SN 7,618 to be a safe drug.

Oxychloroquine (SN 8,137) [62]

General properties and antimalarial activity

The absorption, degradation, distribution, and antimalarial properties of SN 8,137 are essentially similar to SN 7,618 although it appears to have less antimalarial activity in oral dosage. The greater persistence of SN 7,618 in the body is reflected in the smaller weekly dose required of this drug than of SN 8,137 for comparable suppressive effects. The latter appears to be less toxic, but this advantage may be offset by the larger doses necessary for equivalent suppressive action.

The estimated "critical" plasma levels of SN 8,137 necessary for terminating clinical activity and parasitemia due to *P. vivax* and *P. falciparum* have been shown to be approximately 17 and 19 μg. per liter, respectively. In induced experimental malaria, total doses of 0.3 gm. for *vivax* infections and 0.6 gm. for *falciparum* infections have given the mean plasma levels in the order of 25 to 50 μg. per liter in the *falciparum* infections and 17 to 31 μg. per liter in the *vivax* infections. It is apparent therefore that relatively greater doses and higher plasma levels are required for equivalent antimalarial activity than with SN 7,618. Single weekly doses of 0.25 gm. of SN 8,137 for 4 weeks were found effective in suppressing *vivax* (domestic strain) infections transmitted by mosquitoes, whereas weekly doses of 0.125 gm. were ineffective.

No toxicity was reported in 16 volunteers who were given SN 8,137 daily for 6 weeks. The dosage in the sixth week was 600 mg. daily and the total dosage per man during the entire period was 12.2 gm. or an average of 0.3 gm. daily for 42 days. Headache, anorexia, and visual disturbances occurred with moderate frequency in subjects receiving similar amounts of SN 7,618, particularly if the plasma levels were above 275 μg. per liter.

Clinical testing

SN 8,137 had only limited clinical application in the treatment of malaria in the U.S. Army. At Harmon General Hospital, 63 patients with acute attacks of *vivax* malaria were treated with total doses of 2.0 gm. in 3 days (1.0 gm. on the first day and 0.5 gm. on each of the next 2 days). A greater number of patients treated with SN 8,137 had fever on the second day of treatment than had groups treated with SN 6,911, SN 7,618, or quinacrine. Parasite clearance was not as rapid during the first 24 hours of treatment as with quinacrine or SN 7,618, although more rapid than with quinine or SN 6,911. In the next 48 hours, the parasite clearance rate was about the same for SN 8,137 as for the other 4-aminoquinolines as well as quinacrine. Toxic symptoms with SN 8,137 in this study appeared more frequently than with the other synthetic drugs used. There was nausea, vomiting, anorexia,

[62] Formula: 7-Chloro-4-(3-diethylamino-2-hydroxypropylamine) quinoline diphosphate.

and abdominal cramps in a total of four patients, diarrhea in five patients, pruritus in four patients, urticaria and a rash in two patients, and dizziness in four patients.

Although the patients were not retained for determination of the interval to relapse, six patients did relapse within 31 to 39 days after completion of treatment. It appears from this small amount of data that SN 8,137 is inferior to SN 7,618 in its poorer control of fever, slower parasite clearance, shorter interval to relapse, and greater toxicity.

Summary

SN 8,137 has not been studied as extensively as other 4-aminoquinoline compounds. Despite the fact that it appears to have considerable antimalarial activity, although less than SN 7,618, it is doubtful if it offers any advantage over the latter. In the treatment of acute attacks, SN 8,137 proved to be inferior and more toxic than SN 7,618. As a suppressive agent, SN 8,137 may possibly have some value because of its apparent tolerability in relatively large doses. On the other hand, its rapid disappearance from the body compared to SN 7,618 may require doses of an order to offset its alleged tolerability.

Summary of Studies

As a result of extensive clinical and pharmacological studies with these drugs, compounds were found that could be substituted, if necessary, for quinacrine without sacrificing any of the advantages of the latter in the treatment or suppression of malaria. In addition, one of the derivatives of this group of drugs (SN 7,618 or chloroquine) proved superior to quinacrine and other drugs both for treatment and suppression. The 4-aminoquinolines were found to cure *falciparum* infections and to be effective as suppressive agents in single weekly doses. They do not discolor the skin and may be taken for prolonged periods without apparent severe toxicity. The relapse rate in *vivax* infections is not materially influenced by treatment with these drugs, although with SN 7,618 there is a significant prolongation of the interval to relapse and a reduction in the number of short-interval relapses after treatment. Treatment schedules of 1 to 4 days are practical in acute attacks of *vivax* malaria. Extensive field studies of *falciparum* infections were not carried out, and this phase of the treatment of malaria requires further investigation. The occurrence of atypical lichen planus during the prolonged administration of SN 7,618 suggests the possibility of the significant development of this syndrome if chloroquine were to be used as widely as quinacrine. The careful and complete clinical and pharmacological studies carried out with these drugs have added much to knowledge of the chemotherapy of malaria.

8-AMINOQUINOLINE COMPOUNDS

Pamaquine (Plasmochin Naphthoate)[63]

Historical review

The first promising synthetic antimalarial drug was introduced in Germany in 1924, by Schulemann and his coworkers at Leverkusen. The schizonticidal and gametocidal properties of Plasmochin in experimental hosts and in man were such as to represent a major advance in the chemotherapy of malaria. It was hoped that as a result of continued chemical and pharmacological investigations a less toxic and more curative compound would be found. Actually, as will be demonstrated in this section, Plasmochin if properly used produces definitive cure in infections with strains of *P. vivax* that have a high index of repeated relapse after all other forms of treatment. The drug-testing program in Germany continued during World War II and resulted in the synthesis and testing of more than 200 of these 8-aminoquinoline compounds. In the United States, similar activity was directed in a search for an 8-aminoquinoline drug that would be superior to Plasmochin, be less toxic, and might be a true causal prophylactic or curative agent in the prevention, suppression, and treatment of malaria. As a result of these studies, a reevaluation of Plasmochin led to its rational and successful use in curing relapsing *vivax* infections and to the discovery of several compounds that are considered less toxic and in other respects superior to Plasmochin. Certain prewar studies on the clinical application of Plasmochin, reviewed at Moore General Hospital,[64] will be described briefly. In addition, clinical studies made during the war that led to the successful use of Plasmochin as a curative agent will be discussed.

Acute attacks of malaria are more effectively and safely terminated by the use of quinine, quinacrine, or the more recently introduced 4-aminoquinoline compounds than by Plasmochin alone. In recent years, Plasmochin has been used almost entirely as an adjunct to other antimalarial therapy because of its ability to eradicate gametocytes of *P. falciparum* with small amounts of the drug in a matter of a few days. This practice is of questionable value as a control measure in areas where malaria is endemic. There is evidence, however, that simultaneous administration of Plasmochin and quinine daily for 2 weeks or more is highly effective in reducing relapse rates in *vivax* malaria during an observation period of 2 to 6 months. This is in sharp contrast to curative failure or high relapse rates in malaria caused by Pacific strains of *P. vivax* after treatment with quinine, quinacrine, or 4-aminoquinoline compounds.

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[63] Formula (pamaquine naphthoate): methylene-bis-β-hydroxynaphthoate of 6-methoxy-8-(1-methyl-4-diethylamino) butylaminoquinoline.

[64] Most, H., Kane, C. A., Lavietes, P. H., London, I. M., Schroeder, E. F., and Hayman, J. M., Jr.: Combined Quinine-Plasmochin Treatment of Vivax Malaria; Effect on Relapse Rate. Am. J.M. Sc. 212: 550-560, November 1946.

Prewar studies.—Sinton and Bird,[65] in 1928, reported from India on 86 patients given Plasmochin alone or Plasmochin and quinine together for an attack of *vivax* malaria and observed for 2 to 4 months after treatment. Occasionally, patients failed to complete treatment because of toxic reactions or disappearance from observation. The percentage of relapses was calculated on this basis. Twenty-nine patients were given 0.08 gm. of Plasmochin (probably Plasmochin naphthoate) on 17 treatment days during a period of 39 days as suggested by the German manufacturers of the drug. The relapse rate during the period of observation was 36 percent. Twenty-two patients were given 0.08 gm. on as many consecutive days as possible for 28 treatment days with interruptions only for toxic manifestations, the average treatment period being 36 days with a range from 28 to 53 days. The relapse rate in this group was 23 percent. Fifteen patients were given 0.10 gm. Plasmochin plus 1.25 gm. quinine sulfate on 17 treatment days during a 39-day course of treatment. The relapse rate during 2 to 4 months was 20 percent. Finally, a group of 20 patients received these same daily amounts of both drugs for 28 days as continuously as possible during an average treatment period of 37 days. None relapsed during the period of observation. The relapse rate for the 51 patients who received Plasmochin alone was 30 percent and for the 35 patients who received Plasmochin and quinine together, 8.5 percent. Thus, of the total number of 86 patients who received Plasmochin for 17 to 28 days, the relapse rate as given by the authors was 21 percent. This percentage includes 6 patients who were lost to followup studies or who did not complete the full course of treatment and were counted as failures; the failure rate actually observed in 80 men during a period of 2 to 4 months after treatment was 16 percent. In contrast to this finding, the relapse rate for 111 men treated with quinine alone and similarly observed was 77 percent. There is little question that in this study combined quinine-Plasmochin treatment very substantially reduced the incidence of relapse during 2 to 4 months after treatment.

In 1930, Sinton and his coworkers[66] reported two additional groups of patients on combined quinine-Plasmochin treatment for acute attacks of *vivax* malaria. Seventeen were given, daily, Plasmochin, 0.06 gm., and quinine sulfate, 1.25 gm., from 4 to 21 days. None of them had a clinical or parasitemic relapse during 2 months after treatment, when the experiment was terminated. An additional 44 patients received Plasmochin, 0.04 gm., and quinine, 1.25 gm., daily for 21 days. Three patients relapsed, making a total failure rate of 6 percent for 54 men who had Plasmochin for 14 or more days in contrast to a relapse rate of 42 percent for 38 patients who were treated with quinine alone.

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[65] Sinton, J. A., and Bird, W.: Studies in Malaria, With Special Reference to Treatment. Part IX. Plasmoquine in the Treatment of Malaria. Indian J.M. Res. 16: 159–177, July 1928.

[66] Sinton, J. A., Smith, S., and Pottinger, D.: Studies in Malaria, With Special Reference to Treatment. Part XII. Further Researches into the Treatment of Chronic Benign Tertian Malaria With Plasmoquine and Quinine. Indian J.M. Res. 17: 793–814, January 1930.

In 1932, Jarvis[67] reported 8.0 percent relapses during a 2 to 4 months' period of observation of 75 patients who received Plasmochin, 0.03 gm., and quinine, 1.3 gm., daily for 21 days. Manifold[68] reported a study of some 3,000 Indian and British troops treated for acute attacks of *vivax* malaria with Plasmochin, 0.04 gm., and quinine, 1.3 gm., daily for 21 consecutive days. Of these, 98 percent were able to complete the full course of treatment. Analysis of readmission records for 5 months after treatment showed the relapse rate for the whole group was 5.2 percent in contrast to a wide experience of rates from 42 to 77 percent after treatment with quinine alone.

Wartime studies.—In 1945, Kelleher and Thompson[69] reported observations made during the war on the effects of combined quinine-Plasmochin treatment of *vivax* malaria of Mediterranean origin. Of 100 patients with delayed primary attacks treated with 4.6 gm. of quinacrine during 12 days, 34 percent relapsed during an observation period of 5 months. Of 76 patients with delayed primary attacks treated for 10 days with Plasmochin base, 0.03 gm., and quinine 2.0 gm., daily, only 14, or 18 percent, relapsed. The relapse rate for 650 men treated with quinacrine as above for later relapses and followed for 5 months was 34 percent, whereas the relapse rate for 584 men treated for later attacks with combined quinine-Plasmochin was 10 percent. In American experience, the relapse rate in 120 days for Mediterranean *vivax* malaria (150 patients) treated with quinacrine or quinine was 32 percent. There can be no question about the significance of the reduced relapse rate in this British report.

Thus far, references have been cited which indicated that combined quinine-Plasmochin given for at least 10 days, the amounts of Plasmochin base being at least 0.03 gm. a day, is highly effective in reducing the relapse incidence of *vivax* malaria during an observation period of 2 to 5 months. Small amounts of Plasmochin or short-term schedules are definitely of no value in *vivax* malaria of Pacific origin, and experiences with such schedules are generally unconvincing. Dieuaide,[70] in reviewing relapses following various schedules of treatment in the Pacific area, cites 83 percent within 16 weeks for 185 men who had had two courses of quinacrine hydrochloride for acute attacks of *vivax* malaria and 78 percent for 136 patients who had had two consecutive courses of treatment consisting of quinacrine (0.1 gm. three times daily for 7 days), followed by Plasmochin naphthoate (0.02 gm. three times daily for 5 days), after which both were repeated. Thus, Plasmochin for 5 days and repeated a week later was not effective in reducing the relapse rate as compared with quinine or various schedules of quinacrine mentioned

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[67] Jarvis, O. D.: Further Researches into the Treatment of Chronic Benign Tertian Malaria With Plasmoquine and Quinine. Indian J.M. Res. 20: 627–631, October 1932.

[68] Manifold, J. A.: Report on a Trial of Plasmoquine and Quinine in the Treatment of Benign Tertian Malaria. J. Roy. Army M. Corps 56: 321, May; 410, June 1931.

[69] Kelleher, M. F. H., and Thompson, K.: Treatment of Malaria. Lancet 2: 217, 18 Aug. 1945.

[70] Dieuaide, R.: Clinical Malaria in Wartime. War Med. 7: 7–11, January 1945.

by Dieuaide. In the *Bulletin of the U.S. Army Medical Department*,[71] relapse rates are compared for various groups of patients treated in this country for acute attacks of *vivax* malaria of Pacific origin and followed for at least 90 days afterward. Of these, 176 patients were given quinacrine or totaquine alone, and 57 percent relapsed; 299 patients received 0.01 gm. Plasmochin base three times daily for 3 days after quinacrine or totaquine and quinacrine, and the combined relapse rate in all these Plasmochin groups was 56 percent. Here, again, is good evidence that Plasmochin for 3 days after other antimalarial therapy is not effective in influencing the relapse rate of Pacific *vivax* malaria. On the other hand, Gentzkow and Callender,[72] in 1938, reported from Panama that this amount of Plasmochin (0.01 gm. three times a day for 3 days) in addition to 2.4 gm. of quinacrine, during 4 days, given to 128 patients resulted in a relapse rate of 9.4 percent in 6 months compared to 45.6 percent in 215 patients who received quinacrine alone. This report is based on analysis of patient malaria registers. From India, Bird [73] reported 30.9 percent relapses in 152 patients treated with Plasmochin, 0.01 gm. three times a day for 5 days, following 5 to 7 days of quinacrine, and a relapse rate of 46.3 percent for 201 patients who received the same amount of Plasmochin after 7 days of quinine.

Summary.—The evidence that has been cited indicates quite definitely that simultaneous quinine-Plasmochin treatment for 14 days or more of *vivax* malaria of Indian or Mediterranean origin resulted in a very significant reduction in relapse rates during periods of observation of from 2 to 6 months and that Plasmochin for 3 to 5 days after quinine, totaquine, or Atabrine is of no benefit in reducing relapses in *vivax* malaria of Pacific origin. In this connection, it should be borne in mind that the majority of relapses occur within a month after quinine or totaquine treatment and within 3 months after quinacrine or the 4-aminoquinoline drugs. Short-term courses of Plasmochin (3 to 5 days) are of doubtful value in reducing relapse rates in *vivax* malaria of Indian origin, and the reported beneficial effect of 3 days of Plasmochin after quinacrine in reducing relapses in *vivax* malaria of Panamanian origin remains unconfirmed.

Study at a specialty center

The following report from Moore General Hospital, a specialty center for tropical diseases, deals with the effect on subsequent relapse of simultaneous combined quinine-Plasmochin treatment for 14 days in *vivax* malaria of Pacific origin, which had not previously been studied.

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[71] Treatment of Relapses of Vivax Malaria. Bull. U.S. Army M. Dept. No. 89, pp. 21-22, June 1945.

[72] Gentzkow, C. J., and Callender, G. R.: Malaria in the Panama Canal Department, United States Army. II. Results of Treatment With Quinine, Atabrine, and Plasmochin. Am. J. Hyg. 28: 174-189, September 1938.

[73] Bird, W.: Atebrin and Plasmoquine in Treatment of Benign Tertian Malaria. J. Mal. Inst. India 5: 395, 1944.

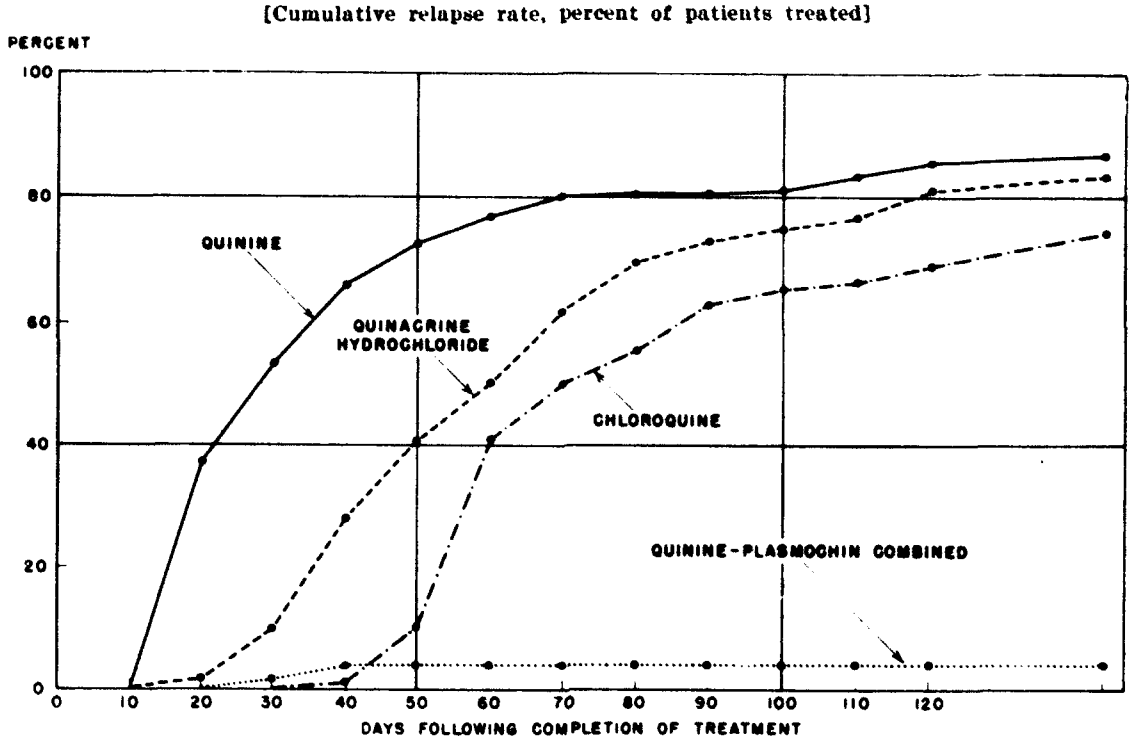
Material and methods.—The protocol described here was furnished by the Office of the Surgeon General. Seventy-two white patients with acute attacks of *vivax* malaria of Pacific origin having fever and positive smears were admitted to a special treatment and study ward. No attempt at selection of patients was made. All drugs were administered by a medical officer. On the first day, quinine sulfate, 1.0 gm., and Plasmochin naphthoate, 0.02 gm. (0.01 gm. base), were given together at 8-hour intervals. On days 2 to 14 inclusive, quinine sulfate, 0.65 gm., and Plasmochin naphthoate, 0.02 gm., were given together at 8-hour intervals. The total amount administered during the treatment period of 14 days was 28.35 gm. of quinine sulfate and 0.84 gm. of Plasmochin naphthoate. A control group of 75 patients with acute attacks of *vivax* malaria of Pacific origin were treated with a total of 28.35 gm. of quinine alone on the same schedule. Temperatures were recorded every 4 hours. Parasite counts were done twice daily until negative for 3 consecutive days. Hemoglobin, methemoglobin, and total white blood count determinations were made daily. (Hemoglobin and methemoglobin were determined colorimetrically as cyamethemoglobin.) Each patient was examined at least once daily by a medical officer, and special attention was paid to possible manifestations of Plasmochin toxicity. On the day after completion of treatment on the ward, the patients were transferred to a convalescent area for further observation. The duration of observation was until relapse or for a minimum of 120 days. During this interval, smears were examined twice weekly. In the event of parasitemia, temperature observations were made every 4 hours and parasite counts were done daily. A temperature of 100° F. or more by mouth in association with a positive smear was considered a clinical relapse.

Results.—The cumulative clinical relapse rates during 120 days' observation after treatment of acute attacks with quinine, quinacrine, and combined quinine-Plasmochin are shown in chart 36. The total failures after treatment are summarized in table 76.

1. ***Quinine.***—Seventy-five patients with acute attacks of *vivax* malaria of Pacific origin were treated with 28.35 gm. of quinine sulfate during 14 days. Sixty-two patients or 82.6 percent had a clinical relapse within 120 days. Five patients who did not relapse had, at one time or another during their period of observation, a positive smear without fever or symptoms. Thus, quinine failed to eradicate the infection in 67 or 89.3 percent of patients treated and observed for 120 days.

2. ***Quinacrine hydrochloride (Atabrine).***—Sixty-nine patients with acute attacks of *vivax* malaria of Pacific origin were treated with 2.8 gm. of quinacrine during 7 days. Fifty-six patients or 81.2 percent had clinical relapses within 120 days after completion of treatment. An additional two patients who did not relapse had, at one time or another during their period of observation, positive smears without fever or symptoms. Thus, within

CHART 36.—*Relapse rates and intervals to relapse after treatment of acute attacks of* vivax *malaria of Pacific origin with various drugs*



120 days following quinacrine, 84.1 percent of treated patients exhibited evidence that they were not cured of the infection.

3. ***Chloroquine diphosphate (SN 7,618).***—Eighty-two patients with acute attacks of Pacific *vivax* malaria were treated with 1.5 to 2.0 gm. of SN 7,618 from 4 to 7 days. Sixty-two or 75.6 percent had a clinical relapse within 120 days after completion of treatment. Four additional patients developed asymptomatic parasitemia without clinical relapse during the 120-

TABLE 76.—*Results of treatment in four groups of patients administered antimalarial drugs for acute attacks of* vivax *malaria of Pacific origin*

Drug	Number of patients	Dosage (grams)	Duration of treatment (days)	Average number of previous relapses	Average prior activity (months)	Clinical relapses[1]		Parasitemic relapses[2]		Total failures[3]	
						Number	Percent	Number	Percent	Number	Percent
Quinine	75	28.35	14	3.8	9.1	62	82.6	5	6.7	67	89.3
Quinacrine	69	2.8	7	4.4	7.8	56	81.2	2	2.9	58	84.1
Chloroquine	82	1.5-2.0	4-7	5.1	10.7	62	75.6	4	4.9	66	80.5
Quinine Plasmochin	72	28.35 0.840	14	5.2	10.6	3	4.2	5	6.9	8	11.1

[1] Clinical recurrence with fever, symptoms, and positive blood smear, observed within 120 days after treatment.

[2] Positive smear only, without fever or symptoms and not followed by clinical relapse during 120 days' observation after treatment.

[3] Clinical relapses plus parasitemic relapses during 120 days after treatment.

day period of observation. In other words, a total of 66 patients or 80.5 percent of the whole number treated represent treatment failures in that they suffered clinical or parasitemic relapses while under observation after treatment with SN 7,618.

4. ***Combined quinine-Plasmochin.***—Seventy-two white patients with acute attacks of *vivax* malaria of Pacific origin were treated with Plasmochin and quinine as described under "Material and Methods." Three clinical relapses occurred within 120 days after completion of treatment, a clinical relapse rate of 4.2 percent. Five additional patients showed parasitemia but had neither fever nor symptoms during the observation period. Thus, of 72 Pacific infections treated, there were altogether only 8 failures, making a total failure rate of 11.1 percent for the 120 days.

Toxicity

Clinical experience.—Numerous references can be found in the literature dealing with toxic manifestations of Plasmochin of varying type and severity. Most frequently reported are gastrointestinal complaints, that is, mild to severe epigastric pain or soreness, anorexia, abdominal cramps, nausea, vomiting, and diarrhea; cyanosis; dyspnea and changes in pulse, in blood pressure and in electrocardiograms; changes in the blood varying from mild anemia to severe or fatal hemolytic crisis or agranulocytosis; vague muscular aches and pains and weakness; and symptoms referable to the central nervous system, principally headache, dizziness, "nervousness," psychosis, and coma. The incidence of severe toxic reactions varies from 1 to 10 percent in different series reported. The hemolytic reaction is the most serious manifestation of Plasmochin intoxication and may vary from mild progressive anemia to a sudden fatal hemolytic crisis associated with shock, severe anemia, jaundice, hemoglobinuria, and azotemia. This reaction may come on early after relatively small amounts of drug but also may occur at any time during the administration of Plasmochin. Weakness and dark urine are the most common symptoms at onset. During the acute episode the erythrocyte sedimentation rate accelerates; the white blood cell count and hemoglobin diminish. Race, diet, climate, and the prior administration of other drugs have all been suggested as factors that may be responsible for initiating a hemolytic reaction. Evidence will be reviewed regarding the possible relation of race to predisposition. The degree of methemoglobinemia in many individuals is probably related to the dose of drug. Gastrointestinal symptoms are most common during the fourth and fifth days of therapy and X-ray studies during this time have revealed gastric hyperperistalsis and intestinal spasm. There follows a brief summary of the incidence of toxic experiences reported in relatively large groups.

Manifold, in a 1931 report[74] dealing with the results of treatment of *vivax* malaria in India with quinine, 1.25 gm., and Plasmochin, 0.04 gm.,

[74] See footnote 68, p. 581.

given together daily for 21 days, noted toxic symptoms or signs occurring in 21 percent of 1,298 British soldiers and in 10 percent of 1,915 Indians treated. Epigastric pain or other gastrointestinal symptoms were complaints in 15 percent of the British and in 8 percent of the Indian patients. Cyanosis was observed in 4 percent of the British cases but was not accurately determined in the Indians because of the color of their skin. Jaundice was observed in only three patients, and in one of these, an Indian, death followed as a result of a severe hemolytic reaction. In Manifold's opinion, the majority of the symptoms were mild. He also emphasized that, of 480 British patients personally treated, the full course of 21 days of Plasmochin was completed without interruption by all but 2 patients. He further stated that 98 to 99 percent of the patients in the entire series of more than 3,000 cases completed a full course of treatment.

West and Henderson,[75] in 1944, reported an incidence of 2.85 percent Plasmochin toxicity in 846 patients treated for *falciparum* infections in Africa with quinine, 2.0 gm. daily for 3 days, quinacrine, 0.3 gm. daily for 5 days, no treatment for 2 days, then Plasmochin base, 0.03 gm. daily for 5 days. Twenty-two of the twenty-four patients with toxic signs had primary *falciparum* infections, and the other two had had malaria and had been treated with Plasmochin previously. Four patients were hospitalized after being given 0.66 gm. of Plasmochin base, and the mean total toxic dose was 0.119 gm. Jaundice was the most common finding and was observed in 20 patients, the mean icteric index being 27.6. Twenty patients had abdominal pain. Headache, weakness, and dizziness occurred in 16, 14, and 11 patients, respectively. Two patients were psychotic and one in coma. There was anemia in 19 patients, and in 1 the red cell count was 1.4 million per cubic millimeter, the average being 2.88 million per cubic millimeter. The white cell counts varied from 4.5 to 20.8 and averaged 10.2 thousand per cubic millimeter. All patients except one were ambulatory during the period of Plasmochin therapy. Unfortunately, the race of the patients or the ratio of black to white in the population sample reported is not stated in this paper.

The color of the skin is of particular interest, as Swantz and Bayliss[76] in 1945 reported moderately severe hemolytic toxic reactions in nine Negroes who had received Plasmochin in the course of treatment for malaria. These reactions were encountered during a period in which approximately 3,000 cases of malaria were treated. The amount or duration of Plasmochin treatment is not stated. As to race, the authors say only that the majority of their malarial patients were white. The absence of a single hemolytic reaction in the whites treated and the occurrence of nine cases of severe intoxication in the Negroes suggest some predisposition to Plasmochin hemolytic reactions in Negroes. In studies summarized by Shannon, 6 hemolytic reactions

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[75] West, J. B., and Henderson, A. B.: Plasmochin Intoxication. Bull. U.S. Army M. Dept. No. 82, pp. 87-99, November 1944.

[76] Swantz, H. E., and Bayliss, M.: Hemoglobinuria; Report of Ten Cases of Its Occurrence in Negroes During Convalescence From Malaria. War Med. 7: 104-107, February 1945.

(5 Negroes and 1 Chinese) were observed among 71 pigmented patients, an incidence of 8.4 percent, but none in 35 white patients who received 0.03 gm. Plasmochin base for from 2 to 14 days. All reactions occurred during the third to fifth days of Plasmochin therapy and were characterized by weakness, dark urine, and icterus at onset.

Hardgrove and Applebaum,[77] in 1945, reported from Panama an incidence of 10.13 percent hemolytic reactions in 4,361 laborers who were given a routine mass treatment for suppression of malaria, the treatment consisting of quinacrine, 0.1 gm. three times daily for 5 consecutive days, no medication for the next 2 days, and then Plasmochin base, 0.01 gm. three times daily, for 5 consecutive days. In 8.12 percent of the whole treated group, the reactions were sufficiently severe to require hospitalization. Three-fourths of these patients were admitted during a 48-hour period corresponding to the last day of Plasmochin treatment and the day following; only 21 toxic reactions occurred following less than 0.10 gm. of Plasmochin base. The principal complaints and findings were abdominal pain, dark urine, anorexia, jaundice, headache, nausea, and vomiting; abdominal tenderness, enlarged liver, pallor, cyanosis, low grade fever, hemoglobinuria, bilirubinemia, anemia, and leukocytosis. Treatment was essentially blood transfusion, intravenous glucose solution, and sodium bicarbonate by mouth. There were no deaths. It should be noted that in this series of patients a large proportion (not precisely stated) were not of the white race; also that the Plasmochin was administered to the men while they were working.

Kelleher and Thompson [78] in their study of 660 British soldiers who were treated for acute attacks of *vivax* malaria with quinine, 2.0 gm., and Plasmochin base, 0.03 gm., daily for 10 consecutive days encountered practically no severe toxic manifestations. Of 295 patients personally treated by the authors, in only 3 was therapy interrupted because of toxicity. Other medical officers participating in the study, having less experience with Plasmochin, interrupted therapy in 2 to 4 percent of 365 subjects. No serious reactions were encountered.

It is evident from this brief survey of the literature that toxic experiences with Plasmochin vary considerably in their incidence and severity. Large groups of patients have been given 0.03 gm. of Plasmochin base for 10 to 21 days with practically no toxicity. On the other hand, serious hemolytic reactions have been reported when the drug was given for only 3 to 5 days. There is evidence that hemolytic reactions occur more frequently in patients who are not of the white race. Some investigators believe that toxic manifestations are more common in patients who have recently received quinacrine. Although it is true that the levels of Plasmochin in the plasma are very much higher in patients who have recently had quinacrine than in patients who have not, it has not been established that high plasma levels and

[77] Hardgrove, M., and Applebaum, I. L.: Plasmochin Toxicity; Analysis of 258 Cases. Ann. Int. Med. 25: 103–112, July 1946.

[78] See footnotes 69, p. 581.

toxicity are related. It seems probable that taking Plasmochin while working may be a factor in producing serious reactions.

The writer (H.M.) and his coworkers administered Plasmochin naphthoate in doses of 0.02 gm. three times daily at 8-hour intervals for 14 days to 100 white patients. No major toxic manifestations were observed, and all patients were able to complete the full course of therapy.

Forty percent of the patients had some form of complaint referred to the gastrointestinal tract and probably related to Plasmochin. These symptoms usually began from the third to the fifth day and lasted from 1 to 7 days; they consisted principally of abdominal cramps or abdominal soreness which were rarely severe.

Cyanosis was observed on the 11th day of treatment in one patient who had a methemoglobin value of 12 percent. Ninety percent of the patients showed methemoglobinemia above normal values at some time during treatment with amounts ranging from 1.0 to 12 percent (average 2.3 percent) of total hemoglobin.

In 16 percent of the patients who were given Plasmochin for 14 days, there was a fall in total hemoglobin of from 11 to 20 percent during the second week of treatment which we considered related to the drug. An equal number of patients had an average fall in hemoglobin of 15.3 percent during the first 5 days. In the latter group, this fall in hemoglobin was apparently due to active malaria rather than to Plasmochin therapy since it occurred in the first few days of the acute attack and reversed itself with continued treatment. Severe anemia did not occur, and no hemolytic crisis was observed.

The effect of Plasmochin on the white blood cell count was to produce leukocytosis in a significant number of men (15 percent with counts above 10,000 per cubic millimeter) during the second week of treatment and leukopenia (24 percent with counts below 5,000 per cubic millimeter) during the first week after discontinuance of the drug. Subsequent counts 2 weeks after treatment were all normal.

In our experience, the toxic manifestations related to the administration of Plasmochin were not severe or serious and should not detract from the value of the drug if proper care is taken in recognizing potentially serious signs of toxicity.

Recommendations for therapeutic use.—It is suggested that patients given Plasmochin as described in this chapter be hospitalized during treatment and observed frequently to recognize early severe hemolysis, should it occur. Treatment with Plasmochin should be limited to white patients. Hemoglobin determinations should be done daily and complete blood counts at least twice aweek. Cyanosis alone is not an indication for discontinuance of therapy. A fall in total hemoglobin of more than 20 percent in any one day should be regarded with suspicion; if followed by a further decline in the amount of total hemoglobin on the next day, Plasmochin treatment should stop. One cannot anticipate sudden hemolysis by any laboratory method,

but symptoms of severe weakness and dark urine during the first 5 days of therapy should be investigated with this possibility in mind. Fluids, blood, and alkalies by vein are indicated if a severe reaction should occur. Abdominal cramps occur most frequently during the first week of treatment and if severe may be controlled with atropine. The usual symptoms of cinchonism, namely, tinnitus, fullness in the head and ears, and headache, were encountered in varying severity in the first week of treatment in the majority of patients. These symptoms gradually subsided in the second week and caused no interruption of therapy. During the first 2 to 5 days of the acute attack of malaria, most patients should remain in bed. For the remainder of the 2-week period of treatment in the hospital, the patients may be ambulant on the ward but should not be permitted vigorous exercise nor be given overnight passes. Each dose of drug must be personally administered by a nurse or physician, and each patient should be seen at least twice daily. Patients with anemia, severely malnourished, or in poor physical condition should not be treated with Plasmochin.

Discussion

The clinical relapse rate of only 4 percent and a total failure of 11.1 percent following combined treatment with quinine and Plasmochin is very striking. In our experience, the clinical relapse in 10 groups of at least 50 patients each has varied from 65 to 85 percent, with total failure rates after treatment of from 75 to 90 percent for all groups except the group treated with quinine-Plasmochin as here reported.

Analysis of more than 1,000 attacks of *vivax* malaria treated and observed at Moore General Hospital for 120 days indicated that within this period of observation the relapse rate for any given attack is not significantly influenced by the number of previous attacks, by the age of the disease (table 76), or by the amount or duration of treatment with quinine or quinacrine. It is unlikely that these factors can account for the wide discrepancy in the observed results. One must also consider what the probability may be of late relapses occurring in the quinine-Plasmochin group after the 120 days' period of observation. The median interval to clinical relapse following treatment with quinine or totaquine is 24 days and following quinacrine or 4-aminoquinoline drugs, 50 to 65 days. Within 120 days, 80 to 90 percent of all patients treated for an acute attack of *vivax* malaria of Pacific origin with currently used antimalarial drugs will have interval parasitemia without fever or symptoms or will actually relapse clinically. We know that a relatively small percentage of failures do occur after 120 days. It is unlikely that absolutely no definitive cures follow treatment with quinine or quinacrine, but even if this were so, the maximum number of failures that could possibly occur after 120 days' observation would be only 10 to 20 percent of treated patients. The median interval to failure (parasitemic and clinical) in the relapses that actually were observed in the quinine-Plasmochin group was 34 days compared to 36 days for the quinine controls. In other words, when

quinine-Plasmochin failed it did so in the same interval after treatment as did quinine alone. Subsequently, we observed 20 percent of the Plasmochin group for at least 180 days after treatment and no failures after 120 days had occurred. Unless Plasmochin alters the biology of *vivax* malaria in man so that very late failures will occur in the majority of treated patients, it is our opinion that the freedom from parasitemia or clinical relapse for 120 days in 90 percent of our treated patients represents definitive cure for at least 80 percent of men so treated.

Analysis of our Plasmochin relapses gives us no clue to a possible explanation for failure. The average mean plasma levels of quinine and Plasmochin are in the same order and range in the failures as in the whole group treated as well as for the patients in whom 120-day cures were observed. There was one failure in nine delayed primary attacks treated. As regards the average age of the disease and the average number of previous attacks, the other seven failures were comparable to the patients in whom treatment was successful.

Clinical use.—Four-month cures in 90 percent of patients treated with combined quinine-Plasmochin raised the question of the general application of this form of treatment for *vivax* malaria. In infections of Mediterranean origin, the relatively low clinical relapse rate of 30 percent within 120 days for *vivax* malaria following treatment with quinacrine or quinine makes it questionable whether routine Plasmochin treatment is indicated in such infections, especially in the second year of the disease. Certain individuals, however, with *vivax* malaria of Mediterranean origin relapse frequently and at short intervals after treatment during the first year of the disease particularly if quinine is used to terminate the acute attack. In these cases, combined quinine-Plasmochin treatment should be considered.

Since 120-day failure rates after treatment of attacks of Pacific *vivax* malaria may be as high as 90 percent, more serious consideration should be given to the use of combined quinine-Plasmochin in this type of infection. Even though there is only a 10 to 20 percent chance that a patient treated with quinine or quinacrine for his first attack will have no subsequent attack in 120 days, it seems worthwhile to take this chance for that attack and possibly for the next one or two relapses. However, the occurrence of repeated attacks, at short intervals, for example, 3 to 6 attacks during the first 6 months of the disease or repeated attacks later in the disease, is in our opinion an indication for the use of combined quinine-Plasmochin therapy. The coexistence of other diseases precluding the use of quinacrine therapeutically or for suppression (quinacrine sensitivity and/or exfoliative or eczematoid dermatitis or atypical lichen planus) is another indication for the use of combined quinine-Plasmochin. Likewise, patients who relapse frequently at intervals of a month or less after quinine and who cannot take quinacrine can be treated with Plasmochin, as outlined. Finally, patients whose convalescence from other diseases is interrupted or delayed by repeated attacks

of malaria should be considered candidates for combined quinine-Plasmochin therapy. Each case must be considered individually and the probability of cure weighed against potential toxicity and a 2 weeks' course of hospital treatment with Plasmochin, compared with a short, safe course of treatment with other antimalarial drugs and the high possibility of failure.

Appreciating the potential dangers of Plasmochin, one is nevertheless impressed by the complete absence of severe or serious toxicity in a series of 100 consecutive white patients who were given 0.06 gm. Plasmochin naphthoate daily for 14 days. The fact that the patients were all white, closely observed in the hospital, and in good physical condition may be factors in the absence of toxicity.

Further study.—Following completion of the study just described, 30 additional white patients with acute attacks of *vivax* malaria of Pacific origin had, in addition to quinine, quinacrine, or SN 7,618, received Plasmochin for 14 days. Information was now available on relapse rates during 120 to 180 days' observation after treatment for more than 100 cases of *vivax* malaria. The observed relapse rate for the group was 4 percent and the total failure rate less than 10 percent. There can be little question about the curative value of Plasmochin.

It is interesting that in a group of 10 men who received Plasmochin for 14 days after 2.2 gm. of quinacrine had been given to terminate the attack, only one relapse occurred during 120 to 180 days' subsequent observation. No relapse occurred in a similar period of observation in another 10 men who received, during the first 4 days of treatment with Plasmochin, a total of 1.4 gm. of SN 7,618 in addition to the Plasmochin, which was given for a total of 14 days. It seems that successful treatment with Plasmochin may be accomplished after the acute attack is terminated with quinacrine or SN 7,618, or by giving either of these drugs simultaneously with Plasmochin for a few days until the acute attack has been terminated and then continuing Plasmochin until it has been given for 14 consecutive days.

It is noteworthy that of the 100 cases successfully treated with Plasmochin there were 20 patients with primary attacks and 19 with only one prior attack. There were only 2 failures in this group of 39 men, or a failure rate of 5 percent. The severity of infection acquired naturally may vary considerably, but all evidence suggests that the age of the disease or severity of infection is of secondary importance in determining the end results of Plasmochin therapy. Likewise, no correlation has been found between Plasmochin plasma levels and success or failure of treatment. On the other hand, total dose and duration of treatment appear to be crucial factors. For example, in a group of 10 men who received combined quinine-Plasmochin treatment for only 10 instead of 14 days, 6 relapses occurred.[79] Similar failures were reported in treatment of primary attacks or relapses if the total dose of Plasmochin was 0.42 instead of 0.84 gm. during 14 days.

[79] Most, H.: Unpublished data.

Summary

The clinical studies on the effect of Plasmochin in definitively terminating *vivax* infections are of the utmost importance in the chemotherapy of malaria. As a result of these carefully controlled experiments, Plasmochin or similar drugs were established with a definite place in the management of relapsing *vivax* malaria. The original observation by James [80] that Plasmochin given in adequate amounts before, during, and after sporozoite infections resulted in cure of *vivax* malaria has been clinically applied. Similar results with domestic and foreign strains of *P. vivax* in protective and therapeutic tests have been reported in the United States. Treatment of primary attacks or relapses resulted in cures in the great majority of cases in which total doses of Plasmochin of 0.84 gm. were given with quinine or other drugs for 14 days.[81]

Extension of these studies has been made with other 8-aminoquinoline compounds. At least one of these, SN 13,276 or pentaquine, has great promise. No clinical studies with this drug were made in the U.S. Army during World War II. However, it has been shown by civilian and Federal research agencies that it will produce a greater number of cures than Plasmochin in primary attacks and relapses of *vivax* infections transmitted by mosquitoes as well as in protective tests. It has also been shown that it may be less toxic.

Summary of Studies

Protective tests and clinical trials conclusively demonstrated the curative properties of this class of compounds. A reevaluation of Plasmochin resulted in the demonstration that if this drug is administered with quinine or other drugs for 14 days *vivax* malaria will be cured in 80 to 90 percent of naturally acquired clinical disease. In contrast, relapse will be forestalled in only 10 to 20 percent of *vivax* infections after treatment with quinine, quinacrine, or the 4-aminoquinolines. The feasibility and safety of administering 0.84 gm. of Plasmochin to white patients was shown, with only minor toxicity occurring. Plasmochin, which has had its "ups and downs" in the story of the treatment of malaria, was shown to have a definite and important position in the management of relapsing *vivax* malaria. As a result of detailed studies of the 8-aminoquinoline compounds, new members of this group have been found which may be so superior to Plasmochin as to end the search for a curative antimalarial drug.

SUMMARY

The magnitude of the malaria problem during World War II can be appreciated only if it is realized that the war was fought in areas where the disease is endemic and that about a half million cases developed in the U.S.

[80] James, S. P., Nichol, W. D., and Shute, P. G.: On the Prevention of Malaria With Plasmoquine. Lancet 2: 341-342, 15 Aug. 1931.

[81] See footnote 64, p. 579.

Army. At the beginning of the war, there was great anxiety with regard to the loss of our sources of quinine, and there was some question concerning the efficacy of quinacrine as a suppressive and therapeutic agent. Our scientific resources were beautifully organized in a search for better antimalarial drugs. Fundamental studies and a rational approach to the problem led to a clear understanding of the optimum methods of using quinine and quinacrine. Newly developed methods made it possible to compare the relative efficiency of various drugs. It was shown that certain sulfonamides could be substituted in extreme emergencies as suppressive agents. Heavy metals on the whole offered little promise. Antibiotics were of no value.

Quinacrine was shown to be superior to quinine for all purposes except possibly for the treatment of fulminant infections with *P. falciparum*. The toxicity of quinacrine was extensively studied; hitherto undescribed reactions, in particular the eczematoid-lichen-planus-dermatitis complex, and aplastic anemia were encountered in a small percentage of cases. In proper dosage, quinacrine was more effective than quinine in terminating acute attacks and in curing those caused by *P. falciparum*, while the proper use of quinacrine for suppression made possible successful military campaigns in highly malarious areas. Mortality from malaria during World War II was negligible principally because of effective treatment and suppression of clinical malaria.

In the search for new drugs, the 4- and 8-aminoquinolines were widely studied. Several (SN 6,911 and SN 8,137) were as effective as quinacrine and if necessary might have been substituted for it. In addition, one was found (SN 7,618 or chloroquine) that was superior to quinacrine. It does not discolor the skin; it could apparently be given with safety over a long time and would produce satisfactory suppression by single weekly doses. These drugs also cure *falciparum* infections. No studies were available on their value in fulminating *falciparum* infections in comparison with quinine or quinacrine.

Finally, the curative properties of the 8-aminoquinoline compounds were demonstrated. Plasmochin was reestablished as a drug of great value in the treatment of relapsing *vivax* malaria in conjunction with quinine, and new compounds were found (SN 13,276 or pentaquine) which may have fulfilled the search for a generally curative antimalarial agent. The final step in progress to the ideal therapeutic will be an agent that is truly chemoprophylactic. Such a drug may be found, which will be safe when taken over long periods and will completely prevent the development of infection.

This is how the matter stood when World War II ended. The momentum of these studies carried over into investigations continued during the postwar years 1946–54. These investigations were for the most part under the auspices of the U.S. Army. A note is appended on this work, as it ties together the whole and brings it to more sharply defined conclusions. This addendum

on postwar research is drawn from a review prepared by Dr. L. H. Schmidt and Dr. G. Robert Coatney.[82]

Postwar Research

At the close of hostilities, it was evident that much work remained to be done with intent (1) to evaluate known but inadequately assessed suppressive and therapeutic agents and (2) to develop new curative drugs. Many investigators who during the war had taken part in the research programs of the Office of Scientific Research and Development (OSRD) retained their interest in the chemotherapy of malaria. It seemed to them that this unfinished business could best be completed within a similar pattern of cooperative effort.

Accordingly, the fruitful period from 1946 to 1954, inclusive, saw investigations in large part conducted with the active participation and support of the armed services. A Malaria Study Section, under the U.S. Public Health Service, recommended grants-in-aid to interested scientific workers at various institutions. They, together with parasitologists and clinical investigators in the Section on Chemotherapy, Laboratory of Tropical Diseases, National Institutes of Health, agreed to coordinate their activities to achieve specified objectives. A joint group known as Investigators in Malaria Chemotherapy met frequently from October 1946 through 1948 to assess progress and plan new activities.

Investigations under OSRD had established the value of quinacrine. Of the compounds that gave promise in preliminary tests or of having even superior qualities, only one, chloroquine, had been tested sufficiently to be recommended for general use. Two other compounds, amodiaquin and oxychloroquine, belonging to the same chemical group, the 4-aminoquinolines, seemed to merit further trial, as did the 4-quinoline-methanols and a small number of naphthoquinones. In addition, there were the biguanides, particularly chlorguanide, made available to OSRD investigators through the scientific liaison between Great Britain and the United States.

It had been recognized also, during the latter years of the wartime studies, that certain prewar work by the British had shown that the old German drug pamaquine (Plasmochin) possessed a property not common to other antimalarial drugs; namely, its ability to cure naturally acquired *vivax* malaria. This recognition led to confirmatory observations and subsequently to a large program involving synthesis, pharmacological study, and clinical evaluation of the 8-aminoquinolines, a program which dominated the last year of OSRD activities in this field. At the end of the war, this effort had led to the development of at least one compound, pentaquine (SN 13,276), believed to be superior to pamaquine.

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[82] Schmidt, L. H., and Coatney, G. R.: Review of Investigations in Malaria Chemotherapy (U.S.A.) 1946 to 1954. Am. J. Trop. Med. 4: 208–216, March 1955.

In the first of the cooperative postwar studies, the naphthoquinones were found to have only a low level of therapeutic effectiveness and gave no evidence, in man or monkey, of prophylactic or curative properties. Of the 4-quinoline-methanols, three compounds were shown to possess no significant advantages over quinine in the treatment of *vivax* malaria. The fourth produced phenomenal lengthening of the relapse interval, but this was associated with the development of photosensitivity. Accordingly, work on all of these compounds was abandoned. In the 4-aminoquinoline group, continued investigation on the long-term suppressive activity of chloroquine, and on the short-term suppressive and therapeutic properties of amodiaquin, showed that these drugs possess similarly high therapeutic and suppressive activity. The effectiveness and tolerability of chloroquine given intramuscularly, and its effectiveness in single doses given orally, were amply demonstrated.

Chlorguanide, the biguanide that had shown considerable promise in preliminary clinical evaluation by British, Australian, and OSRD investigators, was now thoroughly studied in man and experimental animals. Long-term administration was found to be safe. In the body, the drug was degraded extensively to products that, like the parent drug, exhibited activity against simian malaria. Although, as shown by British investigators, one compound was formed that was more active than the parent compound against avian malaria, subsequent work by other British investigators showed that this metabolic product was no more active than the parent drug against infections with *P. falciparum*. In therapeutic and suppressive studies, chlorguanide exhibited a high degree of activity against infections with *P. vivax*, but it was definitely slower than chloroquine in reducing fever and parasitemia. It was further shown that each of the species of avian, simian, and human plasmodia studied acquired a high order of resistance to the drug when exposed to suboptimal doses and that the resistant characteristic of the simian plasmodium could be transmitted unaltered through the mosquito. When produced in sporozite-induced infections, resistance was a property of the erythrocytic parasites only. Infections with chlorguanide-resistant strains responded normally to drugs such as quinine, quinacrine, and the 4-aminoquinolines. Field study in Guatemala confirmed the superiority of chloroquine for suppression in a systematic comparison with chlorguanide.

These various studies had thus established the therapeutic potentialities of both chloroquine and amodiaquin and demonstrated that either drug was superior to chlorguanide in the general management of malaria in man. The work of consolidation was in general complete.

The major new effort of the Investigators in Malaria Chemotherapy was directed toward development of a generally useful drug that would not merely suppress but would cure the relapsing malaria caused by *P. vivax*. This attempt, centered about work on the 8-aminoquinolines, during 1946 and 1947 followed the pattern of the last year of the OSRD program. This involved synthesis of various congeners of pamaquine (Plasmochin), testing for tox-

icity in monkeys, and finally testing of compounds free of neuronal toxicity against *vivax* infections in human volunteers. In addition, efforts were made to define more precisely the activity of pentaquine and the more effective ways of using it.

In 1948, this pattern of work was changed as the result of a demonstration by Schmidt and his colleagues at the Christ Hospital Institute of Medical Research, Cincinnati, Ohio. They showed that infections with *Plasmodium cynomolgi* in the rhesus monkey were the biological and chemotherapeutic counterparts of infections in man with Southwest Pacific strains of *P. vivax*. with essentially complete parallelism in response both to qualitative and to quantitative aspects of drug activity. For the first time, it was possible to carry out toxicological and, particularly, therapeutic studies in an experimental animal with reasonable expectation that the results could be translated in terms of malaria in man.

Collaborating groups of chemists at Columbia University, New York, N.Y., University of Maryland, College Park, Md., and University of Notre Dame, Notre Dame, Ind., synthesized 42 new 8-aminoquinoline derivatives and remade older analogs in quantities sufficient for simian and human studies. Toxicological and curative therapeutic studies were carried out on all of these compounds in monkeys at the Christ Hospital Institute, and 18 of the compounds were selected for human trial at the University of Chicago, Chicago, Ill. Both in man and in monkey, four compounds emerged with properties superior to pamaquine. These were pentaquine and isopentaquine, which had been developed in 1946 and 1947, respectively, primaquine (SN 13,272), and SN 3,883. The last two compounds, with terminal primary amino groups on the side chain, had been prepared during the OSRD program but were subjected to study in man only after investigations at the Christ Hospital Institute had focused attention upon the high tolerability of this class of compounds and their unusual activity against the early and late exo-erythrocytic stages of *P. cynomolgi*.

Between 1948 and 1950, considerable study was also given to the mechanisms for enhancing the effectiveness of known agents. Two observations that proved of practical significance were made at the Christ Hospital Institute and later confirmed in principle in the human subject at the University of Chicago. These observations were (1) quinine had no specific enhancing effect on the curative activities of 8-aminoquinolines such as pentaquine, isopentaquine, and primaquine, and (2) that these drugs could cure and in some cases prevent malaria infections when given alone. It followed that the sole contribution of quinine was the control of erythrocytic infection. This contribution explains the therapeutic effectiveness of Plasmochin combined with quinine; it could be made as well by chloroquine or any other schizonticidal drug, or could be dispensed with if the 8-aminoquinoline were administered, in established infections, in the interval between relapses. This finding formed the basis for the "interim primaquine" regimens which allegedly have

been responsible for the reduced incidence of malaria among troops returning from Korea in 1952 and 1953.

Late in 1950, it was decided to concentrate the cooperative studies upon the relative merits and best use of the four compounds that seemed most promising, pentaquine, isopentaquine, primaquine, and SN 3,883. Evaluation of these drugs in curing established infections with *P. vivax* in volunteers was in part made the responsibility of a group of investigators headed by Dr. Alf S. Alving at the University of Chicago. A second clinical testing facility was established at the U.S. Penitentiary, Atlanta, Ga., under the direction of Dr. Coatney.

In the meantime, the appearance of numerous cases of acute malaria among military personnel returning from Korea demanded more immediate solutions. At a meeting called by The Surgeon General, Department of the Army, on 3 July 1951, it was decided to focus attention upon primaquine and particularly to investigate (1) its effectiveness in eradicating established infections in returnees from Korea and (2) the feasibility of administering 15 mg. daily for 14 days to all servicemen returning from Korea by ship.

The overall safety of this dosage schedule for military men on full duty was demonstrated in a preliminary investigation, involving 1,000 U.S. Army personnel, carried out at Fort Benning, Ga., and Fort Knox, Ky. Beginning on 18 September 1951 with a group of servicemen returning by ship from Korea, the administration of 15 mg. of primaquine daily for 14 days was adopted as a general procedure pending more precise data from the controlled studies underway in the United States. Collateral studies at the University of Chicago showed that daily doses of 30 mg. of primaquine were tolerated by Caucasians; in Negroes, such doses evoked intravascular hemolysis in 5 percent.

Data from the controlled studies on prisoner volunteers, available in January 1952, showed the superiority of primaquine over pentaquine, isopentaquine, and SN 3,833 as a curative drug. The results obtained in active infections with *P. vivax* in returnees from Korea showed the high order of curative effectiveness of primaquine and its superiority over pamaquine (Plasmochin). The effectiveness of interim treatment with primaquine was demonstrated in selected returnees. This composite information, together with toxicological data obtained by study of prisoner volunteers, provided a solid basis for the adoption of interim treatment with primaquine for the cure of *vivax* malaria of Korean origin. This procedure was eventually applied to all military personnel returning by ship from Korea and has been associated with the virtual elimination of malaria among them.

Late in 1950, interest was aroused in a new type of antimalarial drug which had been produced in the Wellcome Research Laboratories, New York, as a by-product of investigations on purines and pyrimidines as carcinolytic agents. Attention centered on pyrimethamine (2, 4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine, Daraprim). Extensive studies were carried out on its

pharmacology in man and lower animals, on its activity against avian and simian malarias, and against infections with *P. vivax* and *P. falciparum*. Therapeutic studies in both lower animals and man showed that the compound had higher activity against erythrocytic parasites than any known antimalarial drug. It was slower, however, than chloroquine in controlling active simian and human infections. It was active against the exo-erythrocytic stages of all species of malarial parasites studied. It was able to effect suppressive cure in a high proportion of infections with *P. vivax*. Resistance to pyrimethamine developed rapidly during inadequate treatment of erythrocytic infections with avian, simian, and human plasmodia. In *cynomolgi* and *vivax* malarias, the resistance characteristic could be transferred unchanged through the mosquito. Pharmacological studies in the monkey demonstrated that repeated administration of pyrimethamine produced significant deleterious changes in the bone marrow, kidney, and adrenal cortex. Tolerability studies in man attested to the safety of the currently recommended doses of pyrimethamine but showed that, at a sevenfold increase in dosage, changes occurred in the bone marrow similar to those exhibited by the monkey.

The capacity of pyrimethamine to function as a suppressive cure strongly recommended its use by U.S. armed services. On the other hand, its potential for inducing resistant strains and its slowness of action in treatment of acute attacks were disadvantages not possessed by chloroquine.

In conclusion, one sees that during the period from 1946 to 1954, inclusive, there were marked developments in the chemotherapy of malaria. The position of chloroquine and amodiaquin in the suppression and treatment of *vivax* and *falciparum* malarias and in the cure of the latter was established firmly. The usefulness and limitations of chlorguanide were defined with reasonable certainty. A generally useful drug for the cure of relapsing infections with *P. vivax* was developed in primaquine, and the value of this agent was proved in both laboratory and field investigations. Finally, a new compound, pyrimethamine, possessing interesting possibilities as a suppressive antimalarial drug, was introduced. The ultimate significance of these developments for worldwide control of malaria remains to be appraised. It seems likely, however, that satisfactory measures are now at hand for suppression, treatment, and cure of all human malarias. This remarkably favorable position of malaria therapy is in marked contrast to the uncertainty of the pre-World War II period. It is a tribute to all who took part in the OSRD and postwar malaria researches.

INDEX

AAF. *See* Army Air Forces.
AAF Regional Hospital, Mitchel Field, 237
AAF Regional Station Hospital No. 1, 233
Abassia, 157
ABBEY, Col. EDWARD A., 501
Abdominal pain, in—
  cutaneous diphtheria, 303
  malaria, 483, 520
  pancreatitis, 36
Abdominal reflexes, in Japanese B encephalitis, 88
Abdominal symptoms, in malaria, 483
Abscess(es):
  brain, 100
  gluteal, 535
  in streptococcal infections, 6
  lung, 45–46
  skin, 220
Acetylsalicylic acid, 76, 438
Aches:
  generalized:
    in dengue, 72, 76
    in Fort Bragg fever, 437
    in malaria, 479, 481
    in meningococcal infections, 253
    in sandfly fever, 56
  muscular, in Q fever, 106
  vague, in malaria, 518
Acidosis, diabetic, 259
Acute respiratory diseases, 2–42
  comparison of morbidity and mortality of, in World Wars I and II, 1
  mode of transmission of, 1
  See also Respiratory tract, diseases.
Adenitis, suppurative, in cutaneous diphtheria, 295
Adenopathy, in dengue, 74
Adjutant General, The, 433
Administrative memorandum. *See* Directives.
Admission rates, for—
  common respiratory infection, 8
  infections due to Vincent's organisms, 5
  primary atypical pneumonia, 20–21, 23
  tuberculosis, 330, 335, 336, 353–354
Admissions, for—
  acute articular rheumatism, 225
  bacterial pneumonia, 27
  bronchiectasis, 45
Admissions, for—Continued
  chronic bronchitis, 43
  encephalitis, 84
  lung abscess, 46
  malaria, 450, 460
  pneumonia, 27, 32
  primary atypical pneumonia, 20–21, 23, 27
  pulmonary emphysema, 48
  rheumatic fever, 229
  spontaneous pneumothorax, 373
  types of Vincent's infection, 5
  See also Hospital admissions.
Adrenal cortex, degeneration of, in fulminating bacteremia, 250
Adrenal glands:
  in epidemic typhus:
    involvement of, 216
    pathology of, 170
  tuberculosis of, 367
Adrenalin, effect of, on suppressive action of Atabrine, 470
Adrenals, hemorrhage into, in fulminating meningococcal bacteremia, 252–253, 255–256, 270–271
Adriatic Sea, 53
Aedes aegypti, 442, 445
  breeding places of, 62, 63, 64, 69
  dengue vector, 59, 61
  flight range of, 64
Aedes albopictus, 445
  breeding places of, 69
  dengue vector, 59
  flight range of, 64
Aedes atlanticus, 442
Aedes canadensis, 442
Aedes hebrideus, dengue vector, 59
Aedes mosquitoes:
  breeding index of, 64–65
  breeding places of, 64, 68
Aedes scutellaris, 59, 66
Aedes scutellaris hebrideus, 62
Aedes vexans, 442
Aegean Sea, 53
Aero-otitis, 1
Aerosols, in control of infection, 6
Africa, 82
Age, factor of, in—
  infectious mononucleosis, 39
  malignant diseases of the lungs, 48

Age, factor of, in—Continued
murine typhus, 222
poliomyelitis, 92, 95
scrub typhus, 119
susceptibility to influenza, 10
tuberculosis, 400, 401, 402
typhus fever, 220
Agent(s), causative, of—
Brill's disease, 201
cerebral malaria, 499
common cold, 3
epidemic typhus, 143
influenza, 10–11
murine typhus, 204, 205
sandfly fever, 52
Agranulocytosis, 200, 263
Air, disinfection of, in control of infection, 6
Air Force Base Unit, 1306th, 453
Air Surgeon, 227
Air Transport Command, 501
1306th Air Force Base Unit of, 453
Air transportation, for tuberculous patients, 342, 379, 380, 381
Airborne Engineer Company, 900th, 452
Airborne infection, methods for reduction of, 6
Airfields. *See* Army airfields.
Airplane spraying, of DDT, in mosquito control, 67, 69
Aitape, 121, 123
Alaska:
outbreaks of influenza in, 13
tuberculosis in, 365
Alaskan Department, tuberculosis in, 365
Albuminocytological dissociation, 300
Albuminuria:
in epidemic typhus, 217
in murine typhus, 222
Alcoholic bouts, factor of, in activating malaria, 480
Algeria, 49, 50, 53, 453, 502
Algid malaria, 486
Algiers, 50
Alkaloids, cinchona. *See* Cinchona alkaloids.
ALLEN, Maj. ARTHUR C., 132, 133, 169, 171
Allergic disorders, 9
Allied Force Headquarters, Mediterranean theater, 495
Machine Records Unit of, 508
Malaria Committee of, 494
ALVING, Dr. ALF S., 597
Ambulation, for rheumatic fever patients, 233
Amebiasis, deaths due to, 243
Amebic dysentery, 491
Amebic hepatitis, 491
Americal Division, 280, 451, 557
"demalarialization" in, 497
malaria in, 458
See also Military units.
American Association for the Advancement of Science, 480
American Civil War, 225, 329, 330
American Medical Association, Council on Pharmacy and Chemistry of, 265
American Red Cross, 344
American Zone, of occupied Germany, 397, 398, 399
Amigen, for typhus patient, 153
ANDERSON, Dr. C. RUSSELL, 136, 195n, 201
ANDREWES, Dr. C. H., 22
investigator of epidemic influenza, 10
Anemia, 496
aplastic, 551–552
in blackwater fever, 486
in malaria, 487, 490, 501, 508
Anesthetics, factor of, in activating malaria, 480
Anorexia:
effect of, on suppressive action of Atabrine, 470
in dengue, 72
in Q fever, 106
in sandfly fever, 56
Antibiotics, 1–2
broad-spectrum, 109, 139, 269
in bacterial pneumonia, 27, 31, 32
in epidemic typhus, 194–195
in malaria, 525
in meningococcal infections, 266–269
in scrub typhus, 136
See also specific names.
Antimalarial drugs, clinical trial of, 525–598
cinchona alkaloids, 531–538
4-aminoquinoline compounds, 559–578
8-aminoquinoline compounds, 579–592
heavy metals, 526–528
penicillin, 525–526
quinacrine hydrochloride, 538–558
sulfonamides, 528–530
Antimony compounds, in malaria, 528
Antitoxin, meningococcal, 265–266
Anuria, in meningococcemia, 253, 262. 263
Anxiety, in rabies, 101
APC capsule, 6
Aphasia, in Japanese B encephalitis, 88

Aplastic anemia, factor of Atabrine in, 551–552
APPLEBAUM, I. L., 587
Arbeitsdienst, 395
Archives of Pathology, 172
Arctic Circle, 396
ARLING, Dr. P. A., 266
ARMBRUST, C. A., Jr., 119
Armed Forces Institute of Pathology, 90, 132, 169, 171, 251, 252, 258, 270, 302, 551
Army:
  British First, 49
  British Second, 154
  British Eighth, 453, 504
  First U.S., 353
  Fifth U.S., 51, 104, 354, 506, 507
  French, 330
  German, 51, 313, 316, 394
  Sixth U.S., 121, 466
  Seventh U.S., 51, 155, 453, 504, 506, 507
Army Air Force Technical School, 11, 29, 30
  epidemic of influenza at, 12–13
Army Air Forces, 228, 334, 354, 379
  regional hospitals of, 233, 237
    designated as rheumatic fever convalescent centers, 233
  rheumatic fever control program of, 227, 237, 238
  tuberculosis in, 343–344
Army Air Forces Letter 25–7, 29 Apr. 1944, 233, 236
Army airfields:
  Boca Raton, 39
  Chanute, 101, 226
  Scott, 20, 226
  Seymour Johnson, 46
  Truax, 20
Army Epidemiological Board, 6, 13, 80, 86, 237, 238, 283
  commissions of, on—
    acute respiratory diseases, 3, 4, 11, 18, 19, 20, 105
    airborne infections, 227
    hemolytic streptococcal infections, 226, 227
    measles and mumps, 34–35
    neurotropic virus diseases, 76, 86, 443
    pneumonia, 28, 29
Army Ground Forces, 228, 343
  Officers' Training Center of, 341
  redistribution station of, 346
Army Group, 21st, 154
Army Institute of Pathology, 90, 132, 169, 251, 252, 302, 551
Army Medical Center, 133, 179, 417, 437
Army Medical Department Research and Graduate School, 138
Army Medical Research and Development Board, 384
Army Medical School, 184, 195
Army Medical Service Graduate School, 447
Army regulations, pertaining to—
  tuberculosis, 375, 387, 388, 406
  venereal diseases, 413, 429
  see also Directives.
Army Service Forces, 29, 343, 354
  circulars of, pertaining to tuberculosis, 387, 394. *See also* Directives, pertaining to tuberculosis.
  general hospitals designated as rheumatic fever convalescent centers by, 233
Army Specialized Training Program, 13
Army Veterinary Service, 95
ARONSON, J. D., 370
Arrhythmia, in rheumatic fever, 231
Arsenicals:
  in malaria, 526
  in syphilis, 418, 419
Arsphenamine, 424
  in malaria, 526
Arthralgia:
  in murine typhus, 221
  in rheumatic fever, 235
Arthritis:
  disability discharge due to, 339
  in rheumatic fever, 231
  of hip, complicating dengue, 75
Arthropodborne virus encephalitides, 79–91
  experience with, during World War II, 83–91
  incidence of, 83
  military history of, 80–83
Artificially cultivated influenza vaccine, immunity with, 11, 13
ASHBURN, P. M., 59
Aspirin therapy, in Q fever, 107
Assam, 127, 281, 312, 452
Asthenia:
  in Q fever, 107
  in sandfly fever, 57
  neurocirculatory. *See* Neurocirculatory asthenia.
Asthma, 43–44
  management of, 43
Asthmatics, fitness of, for duty, 43

Atabrine, 115, 452, 465, 493, 494, 510–511, 529, 583
blood levels of, 468, 473–476, 497
clinical use of:
in *falciparum* malaria, 542–545
in *vivax* malaria, 540–542
concentration of, in blood, 473–476
dosage of, 465, 467, 471, 473, 476, 497, 545–549
schedules for, 466, 494
effect of—
adrenalin on suppressive action of, 470
prolonged administration of, 550–556
withdrawal of, 468–469
effectiveness of:
compared with quinine, 511
under combat conditions, 466, 469
experimental field tests with, 530
general properties of, 539
in *falciparum* infections, 469, 470, 496, 498, 542–544
in *vivax* infections, 469, 470, 472, 540–542, 543
intramuscular injection of, 511, 543
oral administration of, 511
plasma concentration of, 510
research on, 494
short-term administration of, reactions to, 555–558
superiority of, to quinine, 525
toxicity of, 466, 495, 498, 550–558
undesirable effects of, 476–477
untoward reactions attributable to, 553–555
See also Quinacrine hydrochloride.
Atabrine dermatitis complex, 553–555
Atabrine suppressive therapy, 494
continuation of, during rehabilitation periods, 469, 471
contribution of, to troop effectiveness, 477
discipline in relation to, 495
early failure of, 466–468
effect of, on parasite species, 469–470
effect of physical activity upon, 480
effects of withdrawal of, 468–469
institution of, 501
long-term clinical experience with, 471–472
principles of regimen of, 539
result of, 476
study on, 466
toxic reactions to, 495
Atelectasis, in Q fever, 107
Athens, 51, 105
Atlantic, colds contracted during crossing of, 6, 15
ATLAS, L. T., 3
Atropinization, in mumps, 38
Attack rates, for malaria, 454, 455, 456, 457, 458
Atypical lesions of diphtheritic infection, 287–288
See also Diphtheritic lesions.
Atypical Pneumonia Board, European theater, 21, 22
Atypical pneumonia, primary, 16–26
reporting of, 20, 23
See also Primary atypical pneumonia.
Auckland, 279
Aureomycin, effectiveness of, in—
bacteremia, 269
Q fever, 109
meningitis, 269, 273
scrub typhus, 139
Australia, 8, 10, 42, 95, 103, 108, 111, 123, 360, 466, 470, 498, 560, 572, 574
outbreak of dengue in, 60–61
Australian Armed Forces, in New Guinea, 112
Australian General Hospital, 2/9th, 113
Austria, 84
Autopsy findings, in scrub typhus, 115, 116
Auxiliary Surgical Group, 1st, 341
Avertin, 102
Axis Powers, 493
AYCOCK, Col. GEORGE F., 382, 384
Azotemia:
associated with typhus fever, 152, 220
in murine typhus, 222

Babinski's sign, 88
Bacillary dysentery, 243, 491
Backache:
in acute attack of malaria, 481
in murine typhus, 221
Back pain, severe, in poliomyelitis, 94, 97
Bacteremia, 27, 244, 260
diagnosis of, 261
fulminant meningococcal, 244–246, 249–256
antiserum in, 239
rash in, 245–246
symptoms, 244–245
treatment of, 271–273
with adrenal hemorrhage, 252–253
without adrenal hemorrhage, 249–252
transition from, to meningitis, 248–249

Bacteria:
associated with *Corynebacterium diphtheriae*, in cutaneous lesions, 292
relationship of, to virus in common cold, 3
Bacterial pneumonia, 26–32
admissions for, 27
complicating typhus, 220, 222
deaths due to, 243
effect of—
antibiotics on, 31
sulfonamides on, 31
epidemics of, 29
in continental United States, 28–31
in European theater, 31
in Mediterranean theater, 32
in oversea theaters, 31–32
incidence of, 29, 31
introduction, 26–28
See also Pneumonia.
Bacteriological media, for recovery of *Corynebacterium diphtheriae*, 294–295
Bacteriological studies, of diphtheria, 280
Bad Berka, 353
BADGER, Col. THEODORE L., 340, 343, 345, 347, 349
BAGNALL, 324
Baguio, 126
BAIN, 324
BAKER, Col. BENJAMIN M., 280, 496
BAKER, M. P., 491
"Balkan grippe," 25, 105, 106
Balkans, 143
BALL, D., 303
BANCROFT, T. L., 59
Bandicoots, reservoir of Q fever, 108
BANG, 498
Barré, J. A., 301
Bat-transmitted rabies, 102
Battalion aid station, in chain of evacuation, 506
Battalions. *See* Military units.
Battle of Saipan, 279
Battle of Sicily, 50
BAYLISS, M., 586
BAYNE-JONES, STANHOPE, 144, 145, 154, 205
BEARCROFT, W. G. C., 188
Bed rest, in treatment of—
cutaneous diphtheria, 305
rheumatic fever, 232, 233
scrub typhus, 131
spontaneous pneumothorax, 47
tuberculosis, 342
Bedding, oiling of, to reduce airborne infection, 6
BEDSON, Sir SAM PHILLIPS, 22
BELL, E. J., 156
Belsen Concentration Camp, 349
epidemic of typhus fever in, 154, 168
BENGTSON, I. A., 135, 183, 190
BENNETT, B. L., 138, 179n, 190, 208, 210
BENSTED, H. J., 296, 297, 312
Benzine compounds, arsenated, in malaria, 526
Benzoic acid, 196
Benzyl benzoate, for scabies, 432
Berlin, 51, 102, 397, 398, 399
BERMAN, B. B., 322
BERNHARD, W. G., 261
BERRY, J. F., 134
BERRY, M. G., 124
Besançon, 346
Beta hemolytic streptococcus, sulfonamide-resistant strains of, 28
BEYER, Maj. EMIL C., 53
Bhamo, 129
Biak, 66, 125, 282, 298, 307
outbreak of scrub typhus on, 121–122
Bicol Peninsula, 126
BIRD, W., 580, 582
Bismarck Archipelago, 120, 359
Bismuth compounds:
in malaria, 528
in syphilis, 418
Biting habits—
of *Aedes scutellaris*, 66
of *Phlebotomus papatasii*, 53
Bizerte, 24, 49, 354, 453, 502
Black Sea, 52
Blackouts, in relapsing *vivax* malaria, 487
BLAND, Lt. Col. EDWARD F., 125n, 151, 152
Blankenhain, 353
BLEECKER, Maj. PHILLIP B., 502
Blockley, 393
Blood:
concentration of Atabrine in, 473–476
concentration of sulfadiazine in, 262
cultures of, in meningococcal infections, 261
effect of loss of, on suppressive action of Atabrine, 470
examination of, for malarial plasmodia, 489
studies of, in diagnosis of malaria, 489–490
whole, in treatment of malaria, 512

Blood picture, in—
dengue, 74
epidemic typhus, 217
Japanese B encephalitis, 89
Blackwater fever, 470, 496, 508, 517, 532
in malaria, 486
BLAKE, Dr. FRANCIS G., 116, 117, 118, 119
BLANC, Dr. GEORGES, 59n, 210
Blood smears:
parasites in, 476
thick, 507
Blood urea nitrogen, in epidemic typhus, 217, 220
Bloodstream meningococci in, 244, 249
Board for the Coordination of Malarial Studies, 525, 574
Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, 80, 105, 226, 283, 443
Boca Raton Army Air Field, 39
Body lice, epidemic typhus transmitted by, 143
Body temperature. *See* Fever.
Bombay, 26, 135
Bône, 49
Bones, tuberculosis of, 358, 367, 383
Bougainville, 112, 126, 451
Bovine tuberculosis, factor of, in nonpulmonary tuberculosis, 367
BOWDOIN, Dr. CHARLES D., 443
Brachial neuritis, homolateral, in malaria, 485
BRADLEY, B., 59
Bradycardia, 76
in dengue, 74, 75
in Japanese B encephalitis, 89
in sandfly fever, 57
in scrub typhus, 127
BRAGDON, J. H., 491
Brain:
abscess of, 100
due to *Neisseria intracellularis*, 258
in meningitis, 258
involvement of, in—
epidemic typhus, 216
Japanese B encephalitis, 90
murine typhus, 222
reactions in, in epidemic and scrub typhus, 170
Breakthrough, of malaria:
during suppressive treatment, 546, 549
with quinine, 535
with totaquine, 536
Breeding index, of *Aedes* mosquitoes, 64–65
Breeding places:
of *Aedes* mosquitoes, 64, 68
of sandflies, 53
BRILL, NATHAN, 201
Brill's disease, 201–204, 220
clinical picture of, 202
diagnosis of, 202–204
epidemiology of, 202
historical note on, 201–202
incidence of, 202
Brisbane, 61
British Army, 106, 298
cutaneous diphtheria in, 281
diphtheria in, 276, 279
British civilian population, influenza in, 15
British Eighth Army, 453, 504
British experience, with poliomyelitis, 94
British First Army, 49
British Isles, 22, 344, 368
British military forces, tuberculosis in, 399–403
British Second Army, 154
British War Office, 499
British West Indies, 208
Bronchi, tuberculosis of, 369
Bronchiectasis, 44–45
differential diagnosis with tuberculosis, 362
Bronchitis, 1, 2, 18, 26, 483
chronic, 42–44
Bronchogenic carcinoma, 48
Bronchopneumonia, 1, 17, 33, 146–147
See also Pneumonia.
BRONSON, L. H., 300
BRUNS, Col. EARL H., 382
Bruns General Hospital, 380, 384, 386–387
census of tuberculous patients in, 386
designation of, as specialty center for tuberculosis, 381, 386
morale in, 386
orientation department, for tuberculous patients, 389
See also Hospitals, general.
Brushy Creek fever. *See* Fort Bragg fever.
Buchenwald concentration camp, 349, 353
Bulletin of the U.S. Army Medical Department, 283, 374, 428, 582
Bureau of State Services, U.S. Public Health Service, 405
Bureau of Tuberculosis, Department of Health, New York City, 406
Burma, 111, 112, 127, 128, 129, 279, 451
cutaneous diphtheria in, 281–282

BURNET, investigator of epidemic influenza, 10
BURNETT, Capt. HARRY W., Jr., 341
BUSHNELL, Col. GEORGE E., 331, 332
BYLON, DAVID, 59
BYRON, R. A., 118

C-47's, use of, in spraying for mosquito control, 69
Cachexia, 508, 523–524
Caesar's campaigns, malaria in, 449
Cairo, 94, 135
Cairo Fever Hospital, Egypt, 145, 157, 159, 193
Calcutta, 70, 499
CALLENDER, G. R., 582
Calvados, 393
CAMERON, J. D. S., 297, 312
Camp fever. *See* Epidemic typhus.
CAMPINOPÉTROS, Dr. J., 59n, 105
Camps. *See* Military installations.
Campsites, clearing of, as preventive measure against scrub typhus, 122
Canada, 82, 95
Canadian Army:
  tuberculosis in, 403–405
  western equine encephalomyelitis in, 82–83
Canadian General Hospital No. 14, 324
Canal Zone, outbreaks of influenza in, 13
Cape Gloucester, 120, 123
Captured prisoners of war:
  diphtheria in, 278, 315
  medical treatment of, 392–393
  polyneuritis in, 283
  tuberculosis in, 393–396
Carbon dioxide, serum content of, in typhus fever, 152
Carcinoma, bronchogenic, 48
Cardiac malaria, 486
Cardiovascular disease, disability discharge due to, 339
Cardiovascular involvement, in epidemic typhus, 146
Carditis:
  associated with rheumatic fever, 231, 236
  complicating cutaneous diphtheria, 288, 302–303
Care of tuberculous patients, 359
  at Bruns General Hospital, 386
  at Fitzsimons General Hospital, 385
  at Moore General Hospital, 387
Caribbean Defense Command, infectious mononucleosis in, 40
Carrier rate:
  for hemolytic streptococcus, 33
  for nasopharyngeal diphtheria, 313
Carriers:
  in diphtheria, 292
  in malaria, 476
Casablanca, 354
Case histories:
  epidemic typhus, 147–151, 158, 159–162, 165, 166
  Fort Bragg fever, 439–440
  malaria, 517–523
  meningitis, 247, 248
  meningococcal infections, 256
  meningococcemia, 246, 247, 248, 249, 250, 251
  murine typhus, 212
Caserta, 53, 56, 108
CASEY, A. V., 118
CASTANEDA, 202
Catania, 453
Catarrhal fever, in South Pacific Area, 9
CAUGHEY, J. E., 94
Causative agent(s), of—
  Brill's disease, 201
  cerebral malaria, 499
  epidemic typhus, 143
  influenza, 10–11
  murine typhus, 204, 205
  sandfly fever, 52
CELLI, A., 449
Cellulitis, peritonsillar, 4, 7
Centers for treatment of tuberculosis, designation of general hospitals as, 381, 382
  See also Hospital centers.
Central America, 366
Central nervous system:
  effect of Atabrine on, 556–558
  intolerance of, to Atabrine, 498
  involvement of, in—
    epidemic typhus, 216, 220
    Japanese B encephalitis, SS
    malaria, 485–486, 487
    mumps, 38
  syphilis, 100
Central Pacific Area, 453, 454, 460, 496
Cephalin flocculation reaction, in mononucleosis, 39
Cerebral malaria, 130, 470, 484–485, 496, 508, 521–523, 543
  causative agent in, 499
  death due to, 484, 499
  development of, 485

Cerebral malaria—Continued
in India-Burma theater, 498, 499
incidence of, 499
intramuscular injections of quinacrine in, 544
prevalence of, 485
temperature in, 485
Cerebrospinal fluid:
concentration of sulfadiazine in, 262
culture of, in meningococcal infections, 260, 261
meningococci in, 267
Certificate of disability for discharge, 237, 381, 383, 434
See also Disability separations.
Cervical lymphadenitis, effect of sulfadiazine on, 6
Chain of evacuation:
evacuation hospitals in, 506–507
general hospitals in, 507–508
medical battalions in, 506
station hospitals in, 508
Chancroid, 430–431
diagnosis of, 430
treatment of, 431
Chanute Field, 101, 226
Chemical Warfare Service, 69
Chemotherapeutic agents, in common cold, 3
Chemotherapy:
in common upper respiratory infections, 9
in epidemic typhus, 195–200
in gonorrhea, 411, 412
in scrub typhus, 136–137
of malaria, research in:
during World War II, 525–594
postwar, 594–598
Chest pain:
in Fort Bragg Fever, 437
in Q fever, 106, 107
Chief consultants:
in medicine, 293, 321
in tuberculosis, 349, 350
Chill, in—
dengue fever, 72
Fort Bragg fever, 437
meningococcal infections, 245, 253
malaria, 481
Chilliness, in—
Fort Bragg fever, 437
Q fever, 106
sandfly fever, 56
scrub typhus, 111
China, 70, 86, 143, 451
China-Burma-India theater, 99, 364–365 453, 454, 455, 458, 460
common respiratory infection in, 8
cutaneous diphtheria in, 276
dengue in, 70–71
influenza in, 16
malaria in, 452
primary atypical pneumonia in, 26
tuberculosis in, 364–365
Chinese troops:
scrub typhus in, 127–128
tuberculosis in, 364
Chinese unit, 22d Chinese Division, 127
Chloral hydrate, 192
Chloramphenicol, 139, 269, 273
Chlorguanide, 595
Chlorides, serum content of:
in epidemic typhus, 217
in typhus fever, 152
Chloromycetin, 139
Chloroquine diphosphate, 562–563, 584–585
absorption, 562
antimalarial activity of, 562–563
clinical testing of, 563
dosage schedule for, 570
effect of, on relapsing malaria, 567–568
effective plasma concentrations of, 563, 568
general properties of, 562
in *falciparum* malaria, 563, 571–572
in *vivax* malaria, 563, 564, 570–571
relative efficiency of, 569
representative treatment schedules for, 565
studies on suppressive efficacy of, 572–576
study of, at specialty center:
materials for, 564
methods of, 564
results of, 565–568
treatment schedules for, 564
superiority of, over quinacrine, 563
toxicity of, 574–576
Chlortetracycline, effectiveness of, in—
bacteremia, 269
Q fever, 109
meningitis, 269, 273
scrub typhus, 139
Christ Hospital Institute of Medical Research, 596
Chronic bronchitis, 42–44
admissions for, 43
cough in, 42
factor of climate in, 42
management of, 42–43
Chronic malaria. *See* Malaria.

Chronic sinusitis, 1
Cinchona alkaloids:
  cinchonidine, 537
  cinchonine, 537
  comparison of, with Atabrine, 538
  dihydroquinine, 537
  quinidine, 537
  quinine, 531–535
  totaquine, 536
Cinchonidine:
  antimalarial activity of, 537
  comparison of, with quinine, 537
Cinchonine:
  antimalarial activity of, 537
  comparison of, with quinine, 537
Cinchonism, 512, 534
Circular letters. *See* Directives, pertaining to specific subject.
Circulars. *See* Directives, pertaining to specific subject.
Circulatory failure, peripheral, in fulminant meningococcal bacteremia, 271–272
Civil War, American, 225, 329, 330
  malaria during, 450
  tuberculosis in Union Army during, 330
Civilian populations:
  dengue epidemics in, 63
  diphtheria in, 278, 310–312
    transmitted by military populations, 315–319
  influenza in, 15
  Japanese B encephalitis in, 86–89
  malaria in, 502
    in India, 498
  measles in, 34
  pneumonia in, 33
  tuberculosis in, 375
  western equine encephalomyelitis in, 82
Classical signs, of scrub typhus, 130
Clearing station, in chain of evacuation, 506
CLELAND, J. B., 59
Climate:
  effect of, on tuberculosis, 359
  factor of, in respiratory diseases, 7, 42
Clinical aspects, of malaria, 479–492
Clinical attack of malaria, predisposing factors in, 480
Clinical characteristics—
  of epidemic typhus, 143
  of scrub typhus, 111
Clinical course, of—
  dengue, 75
  influenza, 15
Clinical course, of—Continued
  primary atypical pneumonia, 19, 21, 25
  Q fever, 107–108
  sandfly fever, 56–57
Clinical experience, with—
  Atabrine suppressive therapy, 471–472
  epidemic typhus, 145–169
  scrub typhus, 112–132
Clinical features—
  of Japanese B encephalitis, 88
  of Q fever, 106–108
Clinical findings—
  in murine typhus, 208
  in sandfly fever, 51
Clinical information, on rheumatic fever, 230
Clinical manifestations, of dengue, 71–76
"Clinical malaria," diagnosis of, 509
Clinical pattern—
  of common respiratory diseases, 4
  of measles, 32
Clinical picture, of—
  Brill's disease, 202
  common upper respiratory infections, 3
  exudative pharyngitis, 4
  poliomyelitis, 94
  rheumatic fever, 229–231
  scrub typhus, 112, 113, 118, 128
Clinical research, vaccine studies, 138, 139
Clinical study, of scrub typhus, 116
Clinical symptoms, of malaria, 481–484
Clinical trials, of antimalarial drugs, 525–598
  postwar research in, 594–598
Clothing:
  DDT dusted, for protection against lice, 201
  impregnation of, as preventive measure against scrub typhus, 122, 127
COATNEY, Dr. G. ROBERT, 594, 597
Coccidioidomycosis, 1, 47, 439
  complicating tuberculosis, 383
  differential diagnosis with tuberculosis, 362
Codeine, 76, 438
Codeine therapy, in Q fever, 107
Cogon grass, 126
Cold, effect of, on suppressive action of Atabrine, 470
Cold hemagglutination, in primary atypical pneumonia, 19, 22, 23
Colds. *See* Common cold.
Collapse therapy, in tuberculosis. *See* Pneumothorax.
Collecting station, in chain of evacuation, 506

Columbia University, 596
Combat, factor of, in diphtheritic lesions, 286, 312
Combat troops, malaria in:
  rates, 465, 466, 468
  suppressive therapy for, 471
Commissions, of Army Epidemiological Board:
  on acute respiratory diseases, 3, 4, 11, 18, 19, 20, 105
  on airborne infections, 227
  on hemolytic streptococcal infections, 226, 227
  on measles and mumps, 34–35
  on neurotropic virus diseases, 76, 86, 443
  on pneumonia, 28, 29
Committees, of National Research Council:
  on medical research, 525
  on medicine, 420
Common cold, 2
  complications of, 3
  convalescence after, 4
  incubation period of, 3
  mode of transmission of, 1
  seriousness of, in infants, 3
  treatment of, 9
  viruses of, 3
Common upper respiratory infection, 2–9
  admission rate for, 8
  definition of term of, 2
  in continental United States, 5–6
  in oversea theaters, 6–9
  incidence of, 5, 6–9
  introduction, 2–5
  noneffectiveness due to, 5–6
  treatment of, 9
  See also Respiratory tract, diseases.
Communicability, of—
  infectious mononucleosis, 39
  measles, 32
  mumps, 35
  primary atypical pneumonia, 20, 24
  rubella, 41
Communicable diseases. *See* specific diagnoses.
Complement fixation test, in—
  Brill's disease, 203
  epidemic typhus, 183–188
    results of, 184, 185
  Japanese B encephalitis, 83, 86, 89
  lymphocytic choriomeningitis, 100, 101
  malaria, 490
  scrub typhus, 134–135
Complement fixation test, in—Continued
  typhus, 157, 181
Complications, of—
  common cold, 3
  cutaneous diphtheria, 288, 298–303
  dengue, 75–76
  malaria, 484–487
  mumps, 35–37
  rheumatic fever, 234–235
  scrub typhus, 118–119, 131
  tuberculosis, 383
Comte, 143
Concentration camps:
  epidemic typhus in, 154–155
  tuberculosis in, 349–353
Conjunctivitis:
  meningococcal, 259, 260
  mild, associated with scrub typhus, 127
Connor, Maj. Charles A. R., 237
Conseil, 143
Constantine, 453, 502
Consultant in Infectious Diseases, in European theater, 14
Consultant in Medicine, in—
  China-Burma-India theater, 364
  Mediterranean theater, 8
  Office of the Surgeon General, 30
  Sixth Service Command, 29
  Sixth U.S. Army, 466
Consultant in Tuberculosis, Office of the Surgeon General, 389, 398, 406
Consumption. *See* Tuberculosis.
Contact-tracing program, for tuberculosis, 356–357
Contagion, of nonpulmonary tuberculosis, 368
Continental United States. *See* Zone of Interior.
Control:
  of diphtheria, 278
  of rheumatic fever, program for, 237–238
Convalescence, after—
  common cold, 4
  dengue, 72, 75
  Japanese B encephalitis, 89
  primary atypical pneumonia, 21
  Q fever, 107–108
  scrub typhus, 123–125, 131
Convalescent centers for rheumatic fever, hospitals designated as, 233
Convulsion(s):
  Atabrine as factor in, 557

Convulsion(s)—Continued
complication of quinine therapy, 501
following intravenous injections of quinine, 535
in cerebral malaria, 485
in scrub typhus, 131
Cooperative Clinical Studies Group, 418
CORBETT, Maj. AUSTIN J., 116, 125n
Cornea:
edema of, in malaria, 486
ulceration of, in meningitis, 259
Corning fritted glass filter, 445
Corps, II—49, 103, 495, 507
Corps area. *See* Service command.
Corps of Engineers, 359
Corsica, 24, 53, 105, 453, 502
Cortisone, 271, 272
Corynebacterium diphtheriae, 8, 32, 275, 280, 281, 287, 288, 289, 290, 292, 293–294, 295, 296
in skin lesions, 279
Corynebacterium hemolyticum, 319–320
Corynebacterium ovis, 292
Corynebacterium pyogenes, 292
Coryza, 483
in Fort Bragg fever, 437
Cough, in—
bronchiectasis, 45
chronic bronchitis, 42
epidemic typhus, 216
Fort Bragg fever, 437
malaria, 483
murine typhus, 221, 222
Q fever, 106
tuberculosis, 354
Council on Pharmacy and Chemistry, American Medical Association, 265
Counseling, in care of tuberculous patients, 389–390
Course. *See* Clinical course.
Cox, H. R., 156
Cox vaccine, 156
field trial of, 157
Coxsackie virus, 100
CRAIG, C. F., 59
CRAIGIE, J., 156, 183
Craigie vaccine, 168, 183
Cranial nerve palsies, residual of cerebral malaria, 485
Cranial nerves, paralysis of, in meningococcal meningitis, 258
CREW, Maj. ROBERT S., 499
Criteria, for evacuation to Zone of Interior, 508
Crowding of troops, effect of, on incidence of—
meningococcal infections, 241
mumps, 37
respiratory diseases, 7
Cuba, 450
Culex mosquitoes, 82, 122
Culex quinquefasciatus, 442
CULLINAN, E. R., 56
Culture medium(s):
agar, 294
Löffler's, 275, 294
Tellurite, 295
Cultures, *Corynebacterium diphtheriae* in, 293, 294
Cutaneous diphtheria, 275–327
associated with nasopharyngeal diphtheria, 312–315
carditis in, 288, 302–303
clinical findings associated with, 295
complications of, 288, 298–303
cost of, to the Army, 307–308
diagnosis of, 288
methods of, 293–295
directive on, 283
factors favorable for spread of, 312
in South Pacific Area, 279–280
incidence of, 275–278, 297–298
information concerning, 279–283
lesions of:
bacteriology of, 288–293
factors in healing of, 306
morphology of, 288–293
multiplicity of, 286
micro-organism of, 281
military problem of, 275–279
neuritis complicating, 299–302
problems for investigation of, 325–326
Schick reaction in, 296–297
treatment of, 304–307
antitoxin in, 301–302
bed rest in, 305
penicillin in, 305–306
surgical measures in, 306
See also Extracutaneous diphtheria.
Cutaneous lesion(s):
moist dressings in treatment of, 305
of epidemic typhus, histology of, 169–170
role of, in spread of diphtheria, 308–310
surgical measures for excision of, 306
Cutaneous manifestations, of meningococcemia, 246, 248
Cutaneous smears, meningococci in, 261

639243°—63——42

Cyanosis, 529
Czechoslovakia, 84

Dachau Concentration Camp, 180, 197, 220, 349, 350
  epidemic of typhus in, 155
D'AGATI, V. C., 255
DAITZ, Maj. BERNARD D., 389
Dakar, 211, 212
D'ALONZO, C. A., 250
DA ROCHA-LIMA, 143, 156
DAVIS, Maj. WILLIAM A., 154, 168n
Davis-Monthan Field, 233
DAWBER, T. R., 490
DAWSON, Dr. M. HENRY, 226
Days lost from duty. *See* Noneffectiveness.
Deafness:
  in epidemic typhus, 216
  in murine typhus, 221
  residual of scrub typhus, 124
Deatabrinization, 497
Death(s), due to—
  amebiasis, 243
  bacillary dysentery, 243
  bronchitis, 1
  bronchopneumonia, 1
  cerebral malaria, 484, 489
  diphtheria, 243, 276, 277
  encephalitis, 83, 85
  endocarditis, 225
  infectious hepatitis, 243
  influenza, 1, 10
  Japanese B encephalitis, 89
  lobar pneumonia, 1, 243
  lung abscess, 46
  malaria, 243, 450, 460–462, 514
  measles, 1, 32, 35
  meningitis, 7
  meningococcal infections, 242, 243, 251
  mumps, 36
  pericarditis, 225
  poliomyelitis, 243
  primary atypical pneumonia, 21, 243
  rabies, 101
  rheumatic fever, 231, 232
  rheumatism, 225
  scrub typhus, 114, 119, 120, 128, 243
  tuberculosis, 243, 354, 360, 375–377
DDT, 58, 67, 69, 104
  use of, against vector of epidemic typhus, 201
DELAY, P. D., 105
Delirium, in—
  cerebral malaria, 485
  epidemic typhus, 216
  meningitis, 270
Delousing measures, in epidemic typhus, 201
DELP, M. H., 300, 303
"Demalariazation," results of, 496, 497
Dengue, 50, 59–78, 82
  adenopathy in, 74
  as differential diagnosis in malaria, 491
  clinical manifestations of, 71–76
  complications of, 75–76
  convalescence, 72, 75
  course of, 75
  diagnosis of, 72, 76
  differential diagnosis of, 76
  epidemics of, 61, 62–66, 70–71
  incidence of, 60, 63, 65, 67, 68, 70
  investigations of, 76–78
  military importance of, 59, 70, 76
  mode of transmission of, 59
  noneffectiveness due to, 65
  onset of, 72
  outbreaks of, 60–71
  physical signs of, 74–75
  rash in, 72
  symptoms of, 72, 74–75
  treatment of, 76
  vectors of, 59, 61
DEOME, K. B., 105
Department of Health, New York City, Bureau of Tuberculosis of, 406
Dermatitis, exfoliative, associated with Atabrine suppressive therapy, 477
Dermatophytosis, noneffectiveness due to, 37
Desert sore. *See* Cutaneous diphtheria.
DES. MATTHEWS, Lt. Col. EDWARD, 15, 24, 25
Deutsche Militärarzt, 316
Diabetes, complicating tuberculosis, 383
Diabetic acidosis, 259
Diagnosis, of—
  Brill's disease, 202–204
  chancroid, 430
  cutaneous diphtheria, 293–295
  dengue, 72, 76
  diphtheria, 278
  encephalitis, 83
  epidemic typhus, 179–192
  gonorrhea, 410, 412
  infectious mononucleosis, 39
  influenza, 16
  lymphocytic choriomeningitis, 100

Diagnosis, of—Continued
malaria, 482, 489–491, 509
meningococcal infections, 260–261
pancreatitis, 36
poliomyelitis, 94, 97–98
primary atypical pneumonia, 20, 21–22
Q fever, 103, 104
rubella, 41
sandfly fever, 49, 50, 51, 56–57
scrub typhus, 113, 125, 133–136
tuberculosis, 358–359, 361, 362, 364
Diagnostic aids:
in epidemic typhus, 179–192
in murine typhus, 213–215
Diagnostic test for typhus, development of, 179
Diarrhea:
in suppressive malaria therapy, 466, 495, 556
severity of, in *falciparum* malaria, 483
Diet:
in epidemic typhus, 153, 192
for tuberculous patients, 379
DIEUAIDE, Col. FRANCIS R., 283, 581, 582
Digitalis, 479
Dihydroquinine:
comparison of, with quinine, 537
in *vivax* malaria, 537
DILLON, Maj. JOHN A., 500
Dimethyl phthalate, clothing impregnated with, 122, 127
DIMOND, E. G., 303
DINGLE, Dr. JOHN H., 3, 18, 240n
Diphtheria, 279–319
complications of, 298–303
diphtheritic neuritis, 299–302
incidence of, 298–299, 305
deaths due to, 243, 276, 277
directives on, 278, 279, 282, 283. *See also* Directives, pertaining to diphtheria.
epidemics of, 317
faucial, 298
immunization in, 278–279
in combat units, 279, 280, 304, 312, 313, 314
in German prisoners of war, 278, 315
in oversea theaters, 279–282
in the Tropics, 310–312
in Zone of Interior, 282–283
incidence of, 275–278
myocarditis in, 302
nasal, 275
Diphtheria—Continued
nasopharyngeal, 280, 281, 282
associated with cutaneous, 312–315
carrier rate of, 313
penicillin in, 321–325
pharyngeal, 275, 297, 299
summary, 326–327
transmission of, from military to civilian populations, 315–319
See also Cutaneous diphtheria.
Diphtheria antitoxin, 295
Diphtheria carriers, penicillin in treatment of, 322
Diphtheritic lesions:
healing of, 284
morphology of, 284–288
in relation to bacteriology of, 288–293
multiplicity of, 286
Schick reactions of individuals with, 296
Diphtheritic neuritis. *See* Neuritis.
Diphtheritic paronychias, 287
Diphtheritic polyneuritis. *See* Polyneuritis.
Diphtheroids, 294, 297
Diplopia, in cerebral malaria, 485
Directives, pertaining to—
diphtheria:
Circular Letter No. 69, Office of the Chief Surgeon, European theater, 28 Sept. 1945, 278
Medical Circular Letter No. 5, Headquarters, USAFSPA, 20 Oct. 1943, 279
Medical Circular Letter No. 14, Headquarters, USAFSPA, 5 Jan. 1944, 279
TB MED 143, February 1945, 283
Technical Bulletin No. 17, Office of the Chief Surgeon, USAFFE, 23 Oct. 1944, 282
discharge of patients to Veterans' Administration:
War Department Circular No. 109, 26 Apr. 1943, 383
establishment of specialized centers:
Circular No. 456, Army Service Forces, 29 Dec. 1945, 387
Japanese B encephalitis:
TB MED 181, July 1945, 86
TB MED 181, 6 Apr. 1947, 88
lymphocytic choriomeningitis:
Circular Letter No. 107, 21 Oct. 1941, 100, 101
Circular Letter No. 74, 19 Mar. 1943, 100, 101
TB MED 212, 16 Jan. 1946, 100, 101

Directives, pertaining to—Continued
malaria:
Circular Letter No. 6, Office of the Surgeon, NATOUSA, 10 Apr. 1943, 509, 510
Circular Letter No. 10, Office of the Surgeon, NATOUSA, 15 Feb. 1944, 510, 511
Circular Letter No. 21, Office of the Surgeon, NATOUSA, 3 Apr. 1944, 508
Circular Letter No. 32, Office of the Surgeon, NATOUSA, 3 Sept. 1943, 510
Circular Letter No. 33, Office of the Surgeon General, U.S. Army, 2 Feb. 1943, 500
Circular Letter No. 34, Office of the Surgeon, NATOUSA, 14 Sept. 1943, 510, 511
Circular Letter No. 41, Office of the Surgeon, NATOUSA, 29 July 1944, 510
Circular Letter No. 56, Office of the Surgeon General, U.S. Army, 9 June 1941, 465, 499
Circular Letter No. 135, Office of the Surgeon General, U.S. Army, 21 Oct. 1942, 499, 500
Circular Letter No. 153, Office of the Surgeon General, U.S. Army, 19 Aug. 1943, 500, 540, 546
meningococcal infections:
Circular Letter No. 170, Office of the Surgeon General, U.S. Army, 30 Sept. 1943, 242, 261, 269
TB MED 9, 12 Feb. 1944, 266
neurotropic virus diseases:
Circular Letter No. 74, Office of the Surgeon General, U.S. Army, 19 Mar. 1943, 79, 100
Circular Letter No. 107, Office of the Surgeon General, U.S. Army, 21 Oct. 1941, 100
TB MED 181, 1945 and 1947, 86, 88
TB MED 212, 16 Jan. 1946, 79, 100, 101
penicillin:
Administrative Memorandum No. 151, Office of the Chief Surgeon, European theater, 27 Nov. 1944, 321
pleurisy with effusion:
TB MED 71, 28 July 1944, 370
purchase of milk:
Circular No. 40, Headquarters, European theater, 5 Sept. 1942, 368
Directives, pertaining to—Continued
purchase of milk—Continued
Circular No. 72, Headquarters, European theater, 10 Nov. 1942, 368
rheumatic fever:
AAF Letter 25–7, 29 Apr. 1944, 233, 236
Circular Letter No. 144, Office of the Surgeon General, U.S. Army, 7 Aug. 1943, 236
TB MED 97, 29 Sept. 1944, 232, 236
TB MED 112, 1 Nov. 1944, 227
scrub typhus:
Technical Memorandum No. 10, Headquarters, USAFFE, 29 Aug. 1944, 124
streptococcal infections:
Circular Letter No. 16, Office of the Surgeon, NATOUSA, 22 Mar. 1944, 7–8
TB MED 112, 1 Nov. 1944, 227
sulfonamides:
Circular Letter No. 170, Office of the Surgeon General, U.S. Army, 30 Sept. 1943, 242
tuberculosis:
AR 40–1080, 31 Dec. 1934 and 10 Dec. 1943, 406
AR 615–361, 14 May 1947, 375, 388
Circular Letter No. 100, Office of the Chief Surgeon, European theater, 25 July 1944, 342
Circular Letter No. 102, Office of the Chief Surgeon, European theater, 4 Aug. 1944, 342
Circular Letter No. 10, Port Surgeon, New York Port of Embarkation, 26 Mar. 1945, 378, 379
Circular No. 40, Headquarters, European theater, 5 Sept. 1942, 368
Circular No. 41, Office of the Surgeon, NATOUSA, 29 July 1944, 356
Circular No. 72, Headquarters, European theater, 10 Nov. 1942, 368
Circular No. 342, Army Service Forces, 14 Oct. 1944, 394
Circular No. 456, Army Service Forces, 29 Dec. 1945, 387
TB MED 71, 28 July 1944, 370
TB MED 221, 29 Apr. 1946, 388
TB MED 222, 16 May 1946, 389
War Department Circular No. 313, 24 July 1944, 406
War Department Prisoner of War Circular No. 11, 8 Feb. 1944, 393

Directives, pertaining to—Continued
venereal diseases:
AR 40–235, 30 Dec. 1924, 429
AR 40–235, 11 Oct. 1939, 413
Circular Letter No. 18, Office of the Surgeon General, U.S. Army, 10 Mar. 1941, 409, 410, 411, 412, 413, 418, 419
Circular Letter No. 32, Office of the Surgeon General, U.S. Army, 1 Feb. 1943, 414
Circular Letter No. 74, Office of the Surgeon General, U.S. Army, 25 July 1942, 412, 413, 419, 427
Circular Letter No. 86, Office of the Surgeon General, U.S. Army, 18 Aug. 1942, 412
Circular Letter No. 93, Office of the Surgeon General, U.S. Army, 30 Apr. 1943, 427
Circular Letter No. 97, Office of the Surgeon General, U.S. Army, 12 May 1943, 413
Circular Letter No. 129, Office of the Surgeon General, U.S. Army, 22 July 1943, 413, 416
Circular Letter No. 195, Office of the Surgeon General, U.S. Army, 1 Dec. 1943, 409
Circular No. 2, Office of the Surgeon General, U.S. Army, 13 Dec. 1910, 428
Circular No. 3, Office of the Surgeon General, U.S. Army, 3 June 1911, 428
TB MED 3, 11 Jan. 1944, 429
TB MED 9, 12 Feb. 1944, 415
TB MED 16, 6 Mar. 1944, 415
TB MED 48, 31 May 1944, 427
TB MED 96, 21 Sept. 1944, 415
TB MED 106, 11 Oct. 1944, 425
TB MED 157, April 1945, 430
TB MED 196, 20 Aug. 1945, 416
TB MED 198, 20 Aug. 1945, 425
War Department General Orders No. 6, 13 Feb. 1923, 429
Disability separations, due to—
asthma, 44
bronchiectasis, 45
cardiovascular disease, 339
diseases of the ear, 339
duodenal ulcer, 339
meningococcal infection, 270
rheumatic fever, 236, 237
sandfly fever, 55
spontaneous pneumothorax, 47
Disability separations, due to—Continued
tuberculosis, 329, 332, 334–339
Discharge rate, for tuberculosis, 338–339
Disease(s):
deaths from, 1
disability separations for, 332, 339
miteborne, 111–142
of military importance, 59, 70, 76
of respiratory tract, 1–48
Disorientation:
in *falciparum* malaria, 484
in Japanese B encephalitis, 88
Discipline, in relation to Atabrine suppressive therapy, 495
Disposition, change in, in *falciparum* malaria, 484
Disposition, of patients:
after rheumatic fever, 233, 236–237
with asthma, 43–44
with malaria, 516
with scrub typhus, 123–125
with sandfly fever, 53–55
with tuberculosis, 341–342, 355–356
Diuresis, spontaneous, in scrub typhus, 131
Division of Medical Sciences, National Research Council, 94, 136, 493
Committee on Pathology of, 171
Office of Medical Information of, 374
Division of Virus and Rickettsial Diseases, Medical Department Professional Service Schools, 179, 180, 184
Divisions. *See* Military units.
Dizziness:
associated with dengue, 72
following totaquine treatment, 536
Dobodura, 113, 116, 120
DOERR, R., 52
DORLAND, Brigadier, of British Army, 298
Dorsetshire, 23
Dosage, of Atabrine, for effective suppressive therapy, 466–467, 473–476, 497, 498, 545–549
DOWLING, H. F., 263
Dressings, moist, for cutaneous diphtheria lesions, 305
Drinker respirator, 98
Drowsiness, in *falciparum* malaria, 484
Drugs, antimalarial:
Atabrine. *See* Atabrine; Quinacrine hydrochloride.
chlorguanide, 595
chloroquine diphosphate, 562–563, 584–585
clinical trials of, 525–598

Drugs, antimalarial—Continued
effectiveness of, 500–501, 532, 536, 541, 542, 543, 548, 560, 563, 573, 574
Fraxine, 499
oxychloroquine, 577–578
pentaquine, 592, 594
Plasmochin naphthoate, 501, 511, 579–592
primethamine, 598
quinine, 493, 496, 501, 511–512, 531–535
Sontochin, 559–562
Sontoquine, 512
totaquine, 536
toxic reactions of, 501, 536, 550–558, 561, 574–576, 585–589
Ducrey bacillus, 430
DUDLEY, S. F., 292n, 296, 298
DUMAS, J., 59
DUNCAN, Col. GARFIELD G., 466, 498
Duodenal ulcer, disability discharge due to, 339
DURIEUX, 212
Dust, factor of—
in asthma, 43
in Q fever, 105, 108, 109
DYER, R. E., 108, 204
Dyspnea, in—
cutaneous diphtheria, 303
epidemic typhus, 216
relapsing *vivax* malaria, 487

Eagle test, for malaria, 490
Ear, diseases of, disability discharge due to, 339
East Anglia, 15, 41
Eastern equine encephalomyelitis, 79, 82
Echo virus, 100
ECKE, R. S., 157, 159, 197
Ecthyma. *See* Cutaneous diphtheria.
Efate, 451
Egypt, 94, 180, 220, 275, 318
epidemic typhus in, 145
Egyptian Government, Ministry of Public Health of, 145–146, 157
8-aminoquinoline compounds, 579–592
discussion, 589–591
clinical use, 590–591
further study, 591
historical review, 579–582
prewar studies, 580–581
recommendations for therapeutic use, 588–589
study at a specialty center, 582–585
material and methods, 583
results, 583–585
8-aminoquinoline compounds—Continued
summary, 582, 592
toxicity, 585–589
clinical experience, 585–588
wartime studies, 581–582
Elberfeld, 559
El tabardillo (Spanish). *See* Epidemic typhus.
Embaba Hospital, 157
Emirau, 451
Emperor FREDERICK I, 449
Emphysema, pulmonary, 48
Empyema, in lobar pneumonia, 31
Enanthem, of dengue, 72
Encephalitis, 22
complement fixation test in, 83, 89
deaths due to, 83, 85
diagnosis of, 83
epidemics of, 81, 82
Japanese B. *See* Japanese B encephalitis.
lethargica, 80, 89
neutralization test in, 83, 89
resemblance of cerebral malaria to, 485
Russian spring-summer, 79, 82
St. Louis, 79, 81, 88
Venezuelan, 79
Encephalomyelitis, equine, 79, 80, 82, 88
Endemic areas—
of Japanese B encephalitis, 86
of Q fever, 108
Endemic typhus, 204–215
See also Murine typhus.
Endemicity—
of murine typhus, 209
of sandfly fever, 49
Endocarditis:
bacterial, 491
death due to, 225
Enemy military units:
Afrika Corps, 313, 316
15th Panzer Division, 316
21st Panzer Division, 316
England, 7, 9, 15, 16, 17, 23, 38, 42, 344, 349
influenza epidemics in, 14
Enlistment stations, 331
Enterocolitis, tuberculous, 383
Environmental factors, in precipitation of malarial paroxysm, 480
Epidemic(s), of—
dengue:
in Australia, 60–61
in China-Burma-India theater, 70–71
in Hawaiian Islands, 63–65
in New Caledonia, 63

Epidemic(s), of—Continued
dengue—Continued
in New Guinea, 65–68
in New Hebrides, 62–63
in Philippine Islands, 65–68
in Saipan, 68–70
diphtheria, 317
encephalitis, 81, 82
epidemic typhus:
conditions predisposing to, 144
in civilian populations, 145, 155
in concentration camps, 154–155, 169
in Italy, 154
infectious hepatitis, 495
infectious mononucleosis, 40
influenza, 9–10, 11, 12, 14
meningococcal meningitis, 239
mumps, 37
pneumonia, 29
poliomyelitis, 93, 96–97
Q fever, 103–106
in Greece, 105–106
rheumatic fever, 227
sandfly fever, 50, 56
scarlet fever, 226
scrub typhus, 120, 121
streptococcal infections, 227
typhus fever, 143
Epidemic influenza, 10, 11, 14
See also Influenza.
Epidemic parotitis. *See* Mumps.
Epidemic typhus, 143–201
antibodies, 179, 180, 184, 185, 186, 190
Brill's disease following, 201–204
case histories, 147–151, 158, 159–162, 165, 166
causative agent of, 143
clinical characteristics of, 143
clinical experience with, 145–169
in nonvaccinated individuals, 145–155
in vaccinated individuals, 156–169
complications of, 220
diagnosis of:
complement fixation tests with rickettsial antigens in, 183–188
laboratory aids in, 179–192
neutralizing antibody test in, 189–190, 191
rickettsial agglutination in, 188–189
strain isolation and identification in, 190–192
Weil-Felix test in, 179–183
dietary management of patients with, 153
epidemics of, 144, 145, 154–155
Epidemic typhus—Continued
epidemiology of, 143–144
histology of cutaneous lesion of, 169–170
historical role of, 143
immunization in, 156, 163, 164
in concentration camps, 154–155, 169
in Egypt, 145
in French North Africa, 145
in Iran, 145
incidence of, 146
lesion of, 152
metabolic studies of, 152
mode of transmission of, 143
morbidity, 156
neutralizing antibody test in, 189–190, 191
pathological physiology of, 151
pathology of, 169–172
prophylaxis, 201
protective measures against, 156
rickettsiae of, 143
serological findings in, 186, 187
severity of, 146
summary, 215–223
clinical picture, 215–217
diagnosis, 217
immunity, 220
natural course, 220
prophylaxis, 221
relapse, 220
therapy, 221
symptoms of, 146
treatment of, 192–201
antibiotics, 194–195
chemotherapy, 195–200
serotherapy, 192–194
supportive therapy, 192
vaccine:
Cox (U.S. Army), 156–167, 187
Craigie (British Army), 168
Epidemiological study, of scrub typhus, 119
Epidemiology, of—
Brill's disease, 202
Fort Bragg fever, 442
murine typhus, 204–205
Q fever, 108–109
rheumatic fever, 228–229
sandfly fever, 53–55
tuberculosis, 356–357
typhus fever, 143–144
Epidermophyton, 280
Epigastric distress, symptom of totaquine treatment, 536
Epinephrine, effect of, on suppressive action of Atabrine, 470

Equine encephalomyelitis:
eastern, 79, 82
western, 79, 80, 82, 88
Eritrea 95
ERKENBECK, Col. VERNON J., 268
Eruptive fever. *See* Scrub typhus.
Erythema multiforme, 247
in malaria, 517
Erythema nodosum, 438
Eschar:
of cutaneous diphtheria, 284
of scrub typhus, 111, 113, 115, 117, 126
Espíritu Santo, 62, 279, 280, 451
Essential Technical Medical Data reports, 51, 500
Etiological agent, of—
dengue, 59
infectious mononucleosis, 39
Japanese B encephalitis, 86
malaria, 455
Etiology:
of Fort Bragg fever, 443
sandfly fever, 52–53
ETOUSA (European Theater of Operations, U.S. Army). *See* European theater.
Europe, 84, 95, 450
European theater, 91, 99, 102, 410
bacterial pneumonia in, 31
chief consultant in medicine in, 293
diphtheria in, 275, 276
infectious mononucleosis in, 41
influenza in, 14–15
malaria in, 453
measles in, 35
meningitis in, 241
plan for management of venereal diseases in, 425
primary atypical pneumonia in, 21–23
respiratory diseases in, 7, 15
rheumatic fever in, 229
senior consultant in infectious diseases in, 14
shortage of X-ray film in, 391
syphilis in, 422–423, 425
tuberculosis in, 339–353
disposition of patients with, 341–342
hospital admissions, 340
in Army Air Forces personnel, 343–344
in concentration camps, 349–353
in nurses, 342–343
in recovered prisoners of war, 344–349, 391, 392
incidence rates, 339–341
Evacuation:
for poliomyelitis, 98
methods of, 357
of tuberculous patients, 360, 362, 364
general principles of, 378–381
policy for, 342
Evacuation hospitals:
cases of cerebral malaria in, 485
Chinese patients treated in, 499, 500
in chain of evacuation, 506–507
malaria patients in, 506
evacuation policies for, 507
period of hospitalization for, 508–509
role of, in processing liberated prisoners, 350–353
See also Hospitals, evacuation.
EVANS, E. C., 118
EVANS, K. L., 208
Examination(s), at induction:
physical, 45, 331
roentgenographic, 2, 45, 331, 334
Exanthem:
of dengue, 72
of epidemic typhus, 143
Exanthematous typhus. *See* Epidemic typhus.
Exercise tolerance tests, in scrub typhus, 123
Exertion, factor of, in asthma, 43
Exhaustion, factor of, in activating malaria, 480
Extracutaneous diphtheria, 297–298
autoinfection of nasopharynx from skin, 298
incidence, 297–298
Extrapulmonary tuberculosis, 367–370
areas of involvement of, 367
incidence of, 369
Eye, diseases of, disability discharge due to, 339

Facial neuritis, in malaria, 485
Facilities:
diagnostic:
laboratory, 361, 506
X-ray, 361
for reconditioning programs, 235
for study of typhus fever, 145
Fainting, in *falciparum* malaria, 484
FAIRLEY, Brigadier N. HAMILTON, 498
Falciparum infections, studies of chloroquine diphosphate in, 571–572
Falciparum gametocytemia, resistant to Atabrine and quinine, sulfadiazine in treatment of, 512

Falciparum malaria:
acute attacks of, 534, 540
quinine hydrochloride in, 542–545
quinine in, 532
Sontochin in, 560
Atabrine in, 496, 498, 542–545
cerebral symptoms in, 484
chloroquine diphosphate in, 563, 571–574
deaths due to, 461
effect of sulfonamides upon, 528–529
factor of antimony compounds in precipitating clinical attacks of, 528
headache in, 481
intravenous injection of quinacrine in, 544
oxychloroquine in, 577
Plasmochin naphthoate in, 586
quinine in, 532, 534
See also Malaria.
Far East, 154, 525
tuberculosis in, 366–367
Fatality. *See* Death(s).
Fatigability, in relapsing *vivax* malaria, 487
Fatigue:
in activating malaria, 480
in Q fever, 103
Faucial diphtheria, 298
Faucial pillars, swelling of, in nonstreptococcal exudative pharyngitis, 7
Febricula, 55
Feet, defects of, disability discharge due to, 339
FELIX, A., 179
FERRY, N. S., 265
Ferryville, 49, 453, 502
Fever(s):
blackwater, 470, 486, 496, 508, 517–518, 532
catarrhal, 9
control of, 533, 565–566
Fort Bragg, 437–448
pappataci, 506
prolonged, of infectious mononucleosis, 39
Q, 103–109
rheumatic, 225–238
sandfly, 49–58
scarlet, 1, 226, 228, 231
Fever, in—
Brill's disease, 202
common cold, 3, 4
dengue, 72
epidemic typhus, 143
Fort Bragg fever, 437
malaria, 481, 500, 519, 529, 533
meningococcal infections, 253
poliomyelitis, 94
Q fever, 104
rheumatic fever, 231
scrub typhus, 111, 113, 127
Feverishness, in sandfly fever, 56
Fever of undetermined origin, 49, 50, 60, 459
incidence of, 53–55, 503
Fever therapy centers, general hospitals designated as, 412
Fibrosis, pulmonary, 47–48
Field artillery. *See* Military units.
Field hospitals, malaria patients in, period of hospitalization for, 508–509
See also Hospitals, field.
Field Medical Bulletin, 499
Field's stain, in diagnosis of malaria, 509
Fièvre boutonneuse, 109
Fifth U.S. Army, 104, 354, 506, 507
incidence of sandfly fever in, 51
Fiji Islands, 63, 452, 497
FINLAND, M., 23
Finschhafen, 112, 122, 282, 309
First Service Command, 396
First U.S. Army, 353
First World War. *See* World War I.
FISHBERG, M., 372
Fitzsimons General Hospital, 382–386
activity of—
during 1942, 382–383
during 1943, 383
during 1944, 383–384
during 1945, 385
during war period, 385–386
census of tuberculous patients at, 385
designation of, as specialty center for tuberculosis, 381
discharge from, 385
morale at, 385
retirement from, 385
Section for Research on Minimal Tuberculosis of, 379–380, 384
tuberculous captured prisoners of war treated at, 394
See also Hospitals, general.
Fleaborne murine typhus. *See* Murine typhus.
Fleas, in transmission of murine typhus, 204
FLECK, S., 278n, 316
Fleckfieber (German). *See* Epidemic typhus.
FLETCHER, W., 133

639243°—63——43

FLEXNER, S., 239
Flight ranges, of *Aedes* mosquitoes, 64
Floors:
  oiling of, to reduce airborne infections, 6
  sanding of, as preventive measure against scrub typhus, 122
Florence, 103, 104, 105, 502
Fluid balance:
  in meningitis, 269
  in typhus fever, 192
Focus:
  of scrub typhus, 123, 126, 127
  of typhus fever, 143, 204, 205
Fontainebleau, 341
Foodborne streptococcal infection, 8
FORBES, J. G., 312
Formosa, 81, 86, 111
FORRESTER, J. S., 128
Fort Bragg fever, 437–448
  case reports, 439–440
  differential diagnosis in, 441–442
  epidemiological aspects of, 442
  etiology of, 443
  experiments of, 445
  incubation period in, 442, 444
  leukopenia in, 438
  onset of, 437
  rash in, 438
  recognition of, as new disease, 437–440
  special investigation of, 443–446
  symptoms of, 437
Forts. *See* Military installations.
4-aminoquinoline compounds, 559–578
  chloroquine diphosphate, 562–576
  oxychloroquine, 577–578
  Sontochin, 559–562
Fourth Service Command Laboratory, 260
FOX, Brig. Gen. LEON A., 135
Fractions, of penicillin, 426
France, 102, 138, 302, 341, 346, 393, 502
FRANCIS, Dr. THOMAS, Jr., 12
  investigator of epidemic influenza, 10
Frankfurt, 398
FRANZ, K., 52
Fraxine, 499
Frei test, in diagnosis of lymphogranuloma venereum, 431
FRENCH, Lt. Col. ADAM J., 96
French Army, 330
French Morocco, 151, 354
French North Africa, epidemic typhus in, 145
French West Africa, 211–212
Friedländer's bacillus, 27
Fuadin, 432
Fulminant meningococcal bacteremia, 249–256
  case history, 253–254
  clinical course, 253
  Waterhouse-Friderichsen syndrome in, 249, 251, 252, 254–256, 260
  with adrenal hemorrhage, 252–253
  with peripheral circulatory failure, treatment of, 271–272
  without adrenal hemorrhage, 249–252
FULTON, F., 138
F.U.O. *See* Fever of undetermined origin.
Fürsorgestelle, 397
Furunculosis, in epidemic typhus, 147

GALL, E. A., 36n, 37
Gallipoli, 318
Gametocytes:
  action of Atabrine upon, 476
  carriers of, 476, 498
GAMMON, Dr. GEORGE D., 283, 300
Gangrene, in epidemic typhus, 147, 155
Gargliano River, 502
"Garigha" sores. *See* Cutaneous diphtheria.
Gastric ulcer, disability discharge due to, 339
Gastrointestinal symptoms, in malaria, 520–521
Gastrointestinal tract:
  effect of Atabrine on, 501, 556
  effect of quinine on, 534
GAULD, Lt. Col. Ross L., 104, 210n
General hospitals:
  in chain of evacuation, 507–508
  in Zone of Interior:
    antimalarial drug studies in, 536
    cutaneous diphtheria studies in, 282–283
  malaria patients in, 485
    period of hospitalization for, 508–509
    treatment of, 507–508
  tuberculous patients in, 381–388
  See also Hospitals, general.
Geneva Convention, 395, 396
Genitourinary tract:
  diseases of, disability discharge due to, 339
  tuberculosis of, 358, 383
GENTZKOW, C. J., 582
Geographic distribution, of scrub typhus, 111, 112
Gerbilles, 136
Gerbillus gerbillus, 135, 192
Gerbillus pyramidum, 135, 192

GERHARD, 143
German Army:
  diphtheria in, 316
  sandfly fever in, 51
German measles. *See* Rubella.
German military units. *See* Enemy military units.
German prisoners of war, 315
  See also Captured prisoners of war.
German Sanitätsdienst, 396
Germany, 102, 154, 155, 180, 278, 302, 433, 559, 579
  diphtheria in civilian populations in, 316
G.I. Bill of Rights, 390
Giddiness, residual of scrub typhus, 124
Giemsa stain, in diagnosis of malaria, 509
GILDEMEISTER, E., 189, 190
GILLIAM, A. G., 193
GILYARD, Maj. RICHARD T., 102
Gimbaru, 87
Glands:
  adrenal, 216
  lymph, 39
  parotid, 35
Glucosulfone sodium, 382
Gluteal abscesses, 535
Glycols, in air disinfection, 6
Glycosuria, spontaneous, in meningococcal meningitis, 259
GOCHENOUR, W. S., Jr., 447
GOLDBERG, B., 332
GOLDBERGER, 201
GOLZ, Lt. Col. HAROLD H., 502, 514, 521
Gonococcal infections, noneffectiveness due to, 37
Gonorrhea, 410–418
  directives on, 413, 414
  fever therapy for, 412, 413
  management of, 410, 411, 412
  sulfonamide-resistant, 412, 413
  test for cure of, 411
  treatment of:
    chemotherapy in, 411, 412
    on duty status, 413–414
    penicillin in, 414–418
Goodenough Island, 112, 120
GORDON, H. H., 481
GORDON, Col. JOHN E., 21, 102
Gräfelfing, 302
Granuloma inguinale, 432
Great Britain, 102, 349
Greece, 25, 103, 108, 180
  outbreak of Q fever in, 105–106
Green Island, 451
GREIFF, D., 194, 195, 196, 197
Grottaglie Air Base, 106
  See also Army airfields.
GROW, Col. JOHN B., 382
Guadalcanal, 359, 360, 451, 452, 468, 469, 496, 497
Guadalcanal campaign, 280
Guam, 86
Guatemala, 595
GUILLAIN, G., 301
Guinea pigs, in isolation of typhus fever organisms, 191–192
GUNTHER, C. E. M., 112, 113, 483

HAAGEN, E., 189, 190
Haffkine Institute, 135
Halifax, 240
HALL, M. W., 59
HALLMANN, 51
HAMILTON, H. L., 190, 195
Hamilton Field, 380
HAMMAN, L., 47
Hammer Field, 233
HAMMON, Dr. WILLIAM McD., 82, 87
Hankow, 70
HARDGROVE, M., 587
Harvard University, 39
HASHIMOTO, HAKUJU, 111
HASHINGER, E. H., 300
Hassin chifusu (Japanese). *See* Epidemic typhus.
HAVENS, 204
Hawaii, 213, 364
  outbreak of dengue in, 63–65
  outbreaks of influenza in, 13
Hawaiian Islands, 63–65, 363, 364
HAYMAKER, W., 90
Headache, in—
  Brill's disease, 202
  dengue, 72, 76
  epidemic typhus, 143
  malaria, 481, 487
  meningococcal bacteremia, 245, 253
  murine typhus, 221, 222
  poliomyelitis, 97
  Q fever, 106
  sandfly fever, 56
  scrub typhus, 111
Healing of diphtheritic lesions, 284
Health Organization, League of Nations, 429
Heanza Shima, 86
Heart disease, valvular, chronic, complication of rheumatic fever, 234
Heatstroke, 252

Hemagglutination, cold, in atypical pneumonia, 19, 22, 23
Hematuria, in meningococcemia, 262, 263, 269
Hemiplegia, residual of cerebral malaria, 485
Hemolytic streptococcus, 4, 28, 32, 226
  beta, 8, 13, 275
  carrier rate, 33
  group A, 226, 259
  in common respiratory infection, 2
Hemophilus ducreyi, 430
Hemophilus influenzae, 3, 7, 27, 32
  in common upper respiratory infection, 7
Hemorrhage, in adrenal glands, 270
Hemorrhagic nephritis, complicating dengue, 75
HENDERSON, A. B., 586
Henley-on-Thames, 393
Hepatic dysfunction, in malaria, 491
Hepatitis, 7, 16
  infectious, 57, 68, 103, 345, 491
    epidemic of, 495
    factor of, in activating malaria, 480
  noneffectiveness due to, 37
Hepatomegaly, in malaria, 482–483, 519
Herpes labialis, in malaria, 484, 517
Herpes simplex, in meningococcemia, 246
Herpes zoster, in meningococcemia, 246, 258
HERRELL, W. E., 415
HERRICK, W. W., 239, 244
HERTIG, Maj. MARSHALL, 53
HILLMAN, Brig. Gen. CHARLES, 93, 95
Hinton test, for malaria, 490
Historical note, on—
  Brill's disease, 201–202
  malaria, 449–451
  meningococcal infections, 239–240
HITCHENS, A. P., 59
HODES, H. L., 86
HODGES, J. J., 266
Hodgkin's disease, 491
Hollandia, 66, 121, 282
HOLMAN, D. V., 259
Honolulu, 63
Hospital admissions, for—
  malaria, 503
  meningococcal infections, 239, 241
  rheumatic fever, 227
  scrub typhus, 116, 122, 128
  spontaneous pneumothorax, 47, 373–374
  tuberculosis, 329, 334, 340, 354, 364, 367
  typhus fever, 146
Hospital Center, 814th, 138
Hospital ships, for evacuation of tuberculous patients, 357, 378
Hospitalization:
  period of, for—
    dengue, 75
    malaria, 504, 506–509
    sandfly fever, 57
  for tuberculosis, 359
    in Zone of Interior, 378–390
Hospitals, evacuation:
  2d, 41
  14th, 499
  15th, 357
  30th, 120, 268
  48th, 365, 499, 500, 501
  59th, 155, 165
  73d, 499, 500, 501
  77th, 49
  92d, 122
  116th, 155
  127th, 350
Hospitals, field:
  15th, 103, 104
  26th, 458
  77th, 345
Hospitals, general:
  named:
    Baxter, 282, 301
    Birmingham, 229, 233, 236
    Brooke, 97
    Bruns, 380, 381, 384, 394
    Bushnell, 536
    Fitzsimons, 45, 347, 380, 381
    Foster, 229, 233, 236
    Glennan, 394, 395
    Harmon, 282, 293, 296, 304, 306, 309, 479, 481, 488, 490, 553, 560, 563, 570, 577
    Kennedy, 536
    Letterman, 48, 283, 309, 360, 391
    Moore, 282, 292, 296, 304, 553, 563, 570, 573, 579, 582, 589
    Percy Jones, 45
    Sternberg, 93
    Torney, 229, 233, 237
    Walter Reed, 417, 446
  numbered:
    6th, 151, 354, 355
    7th, 23
    9th, 282, 298
    12th, 507
    13th, 282, 309
    17th, 354, 515, 516

Hospitals, general—Continued
numbered—Continued
20th, 127, 128, 137, 281, 295, 299, 300, 302, 309, 313, 452, 499, 501, 534, 544, 549, 572
24th, 24, 354
30th, 38
33d, 511
38th, 94
39th, 279, 280, 287, 307, 308
46th, 346, 349
54th, 282, 307
64th, 354
69th, 281, 297, 299, 313
105th, 123, 282, 491
118th, 490
327th, 393
8274th (Provisional), 393
Hospitals, station:
7th, 513
31st, 536
90th, 124
118th, 511
122d, 280, 298
159th, 499
182d, 502, 512, 516
225th, 502, 512
233d, 123
304th, 393
334th, 393
362d, 118
363d, 116, 120
365th, 341
7029th, 393
Host factors, in precipitation of malarial paroxysm, 480
HOWELL, W. L., 123
HOYNE, A. L., 265
Human beings, as test subjects. *See* Volunteers.
Human transmission experiments:
in Fort Bragg fever, 445, 446
of primary atypical pneumonia, 18, 19, 20
Hydration, in chronic malaria, 487
Hygienic Institute, Dairen, Manchuria, 195
HYMAN, A. S., 491
Hyperhidrosis, in cutaneous diphtheria, 295
Hyperthyroidism, 484
Hypoesthesia, residual of scrub typhus, 124
Hypochloremia, associated with typhus fever, 152
Hypoglycemia, 272
Hypopotassemia, 272
Iceland, 341
I. G. Farben Werke, 559
Immune military personnel, totaquine for treatment of malaria in, 536
Immunity, to—
influenza, 11, 13, 14
lobar pneumonia, 31
measles, 32
poliomyelitis, 93, 95
sandfly fever, 55–56
scrub typhus, 138–139
Immunization:
in diphtheria, 278–279
in lobar pneumonia, 30
in measles, 34
in scrub typhus, 137–138
schedule of, in typhus fever, 156
Incidence, of—
allergic disorders, 9
arthropodborne virus encephalitides, 83
common respiratory infections, 6–9
fevers of undetermined origin, 53–55, 503
meningococcal infections, 241–244
pneumonias, 20, 29, 31
pulmonary diseases, 2, 340, 341, 371
streptococcal infections, 7
See also specific diagnoses.
Incubation period, of—
common cold, 3
diphtheritic neuritis, 301
Fort Bragg fever, 444
murine typhus, 221
primary atypical pneumonia, 24
Q fever, 104–105
rabies, 101
scrub typhus, 123
India, 26, 70, 127, 135, 451, 453, 499, 549, 560, 571, 574, 580, 582, 585
India-Burma theater, 284, 543
establishment of, 499
malaria in, 498–502
scrub typhus in, 127–132
Indian Medical Service, 498
Indigestion, in relapsing *vivax* malaria, 487
Indochina, 111
Indonesia, 493
Inductees, meningococcal infections in, 241
Induction stations, 331
tuberculosis discovered during examinations at, 405
Infantry divisions, Atabrine suppressive therapy for malaria in, 497
See also Military units.

Infantry regiments:
malaria in, 471, 496, 497
Q fever in, 104
scrub typhus in, 121
See also Military units.
Infants, common cold in, 3
Infection(s):
airborne, methods for reduction of, 6
common upper respiratory, 2–9
meningococcal, 239–273
streptococcal, 7
Vincent's, 8, 9, 41
Infectious encephalitis:
admissions for, 84
deaths due to, 85
See also Encephalitis.
Infectious hepatitis:
deaths due to, 243
epidemics of, 495
in recovered prisoners of war, 345
See also Hepatitis.
Infectious mononucleosis. *See* Mononucleosis, infectious.
Inflammation of joints, in meningococcal infections, 245, 259
Influenza, 1, 9–16, 57
antibodies, 11, 13, 14
causative agents of, 10–11
clinical characteristics of, 12
clinical studies of, 12
course of, 15
deaths due to, 10
diagnosis of, 16
differential diagnosis of, 76
epidemics of, 9–10, 11, 12, 14
immunity to, 11, 13, 14
in China-Burma-India theater, 16
in European theater, 14–15
in Mediterranean theater, 15–16
in Pacific areas, 16
in Zone of Interior, 12–13
incidence of, 7, 10, 12, 13, 15, 49
introduction, 9–12
recognition of, 9
serological studies, 12
susceptibility to, 11, 13
vaccination for, 13
virus of, 2
INGRAHAM, Dr. HOLLIS S., 134n, 315
Inland Sea, 81
Inner Reich, 166
Insomnia:
in dengue, 72, 76
in relapsing *vivax* malaria, 487
Institute for the Control of Syphilis, 433
Insulin, effect of, on suppressive action of Atabrine, 470
Interpandemic influenza, 10, 11, 12, 14
See also Influenza.
Invalidism, 32
chronic, in primary atypical pneumonia, 21
Investigations:
of pathology of epidemic typhus, 169–172
postwar, of antimalarial drugs, 594–598
Investigators in Malaria Chemotherapy, 594, 595
Iran, 366
epidemic typhus in, 145
Iridocyclitis, in malaria, 486
Iron, in treatment of malaria, 512
IRONS, E. N., 119
Isigny, 393
Italian prisoners of war. *See* Captured prisoners of war.
Italy, 8, 24, 25, 53, 103, 105, 106, 107, 108, 194, 283, 354, 451, 459, 512, 514
sandfly fever during invasion of, 50
Iwo Jima, 363, 497

JACKSON, E. B., 138
Jail fever. *See* Epidemic typhus.
Jamaica, 208
JAMES, C. S., 284
JAMES, S. P., 592
Japan, 81, 87, 111, 128, 155, 447
tuberculosis in native population of, 366
Japanese Anti-Tuberculosis Association, 366
Japanese B encephalitis, 79, 81
antibodies, 87
clinical features of, 88
convalescence following, 89
differential diagnosis of, 89
directives on, 86, 88
laboratory findings, 89
outbreak of, on Okinawa, 86–89
pathology of, 90
signs of, 88
supportive measures for, 90
symptoms of, 88
therapeutic measures for, 90
vaccine for, 90
Japanese prisoners of war. *See* Captured prisoners of war.

Japanese river fever. *See* Scrub typhus.
Japanese troops, scrub typhus in, 128
JARVIS, O. D., 581
Jaundice, associated with malaria, 519
Jefferson Barracks, 20, 45, 101
See also Military installations.
JOBLING, J. W., 239
JOHNSON, A. S., Jr., 124
JOHNSON, J. W., Jr., 52
Joint fever. *See* Dengue.
Joints:
inflammation of, in meningococcal infections, 245, 259
involvement of, in rheumatic fever, 230, 235
pain in, in meningococcal infections, 245, 253
tuberculosis of, 358
JORDAN, A. C., 261
Josiah Macy, Jr. Foundation, 237
Jungle rot. *See* Cutaneous diphtheria.
Jungle warfare:
malaria suppressive therapy, under conditions simulating, 497
scrub typhus as medical problem of, 112

Kahn test, 40, 490
Kala-azar, 528
KAPLAN, A., 76
Karachi, 453
KARELITZ, S., 321n, 322
KASTLIN, Col. GEORGE J., 386
Kedani fever. *See* Scrub typhus.
KEEFER, C. S., 266
Keesler Field, 233
KELLAM, J. W., 278n, 316
KELLEHER, M. J. H., 581, 587
KELSER, Brig. Gen. RAYMOND A., 81
KERN, R. A., 482, 483n
Kidney:
effect of Atabrine on, 550–551
tuberculosis, 359, 369
KING, Col. DONALD S., 355
KINGSBURY, Maj. LAWRENCE H., 386
KINSMAN, Lt. Col. J. MURRAY, 250n, 387
Kline test, 490
KLIPPEN, A. J., 278n, 316
KNEELAND, Col. YALE, Jr., 21
KOCHER, R. A., 324
Koh's block test, 557
KOLMER, J. A., 266
Kolmer test, 490
Korea, 86, 88, 155, 597
Kuder Preference Record, 390
Kunai grass, 120, 121

Laboratory(ies). *See* Medical General Laboratory.
Laboratory aids, in diagnosis of—
epidemic typhus:
complement fixation tests, 183–188
Weil-Felix test, 179–183
Japanese B encephalitis, 89
lymphocytic choriomeningitis, 100
murine typhus, 213–215
scrub typhus:
complement fixation tests, 134–135
isolation of strains, 135–136
Weil-Felix reaction, 133–134
Laboratory facilities, for—
detection of tubercle bacilli, 358
diagnosis of Japanese B encephalitis, 90
diagnosis of tuberculosis, 361
Laboratory findings, in—
Japanese B encephalitis, 89
murine typhus, 208
Q fever, 108
scrub typhus, 130
Laboratory procedures, in diagnosis of malaria, 489–491, 509
blood studies, 489–490
complement fixation test, 490
parasite identification, 489
serological tests, 490–491
Lae, 120
Lancet, 22
Laoag Army Air Base, 96
See also Army airfields.
Laparotomy, in malaria, 520
LAPLACE, Col. LOUIS B., 394, 395
Laruma River, 126
Laryngitis, tuberculous, 383
Larynx, tuberculosis of, 369
Las Vegas Army Air Field, 233
Latin America Area, tuberculosis in, 366
LAUFER, M. W., 299n, 300
LAWRENCE, Maj. EDGAR A., 501
LAWSON, Col. HERMAN A., 500
League of Nations, Health Organization of, 429
Ledo, 127, 281, 452
Ledo Road, 128
Leghorn, 354
Le Havre, 345
LEIFER, W., 419, 420
Leishmania, 280

Leishmaniasis, 491
LENNETTE, E. H., 105
LEPPER, M. H., 263
Leptospira, 447, 448
Leptospira autumnalis, 447, 448
Leptospiral meningitis, 76
Lesions, harboring *Corynebacterium diphtheriae*, characteristics of, 284–288
LESSLAR, J. E., 133
Lethargy, in Japanese B encephalitis, 88
Letterman General Hospital, 391
See also Hospitals, general.
Leukemia, acute, 252
Leukocytes, diplococci in, 260, 261
Leukocytosis, 17
in Fort Bragg fever, 438
in malaria, 489
in meningococcemia, 246
in respiratory infections, 9, 13
Leukopenia, 200
in dengue, 74
in Fort Bragg fever, 438
in malaria, 489
in sandfly fever, 57
Levin tube, 269
LEVINE, H. D., 123
LEWIS, L., 88
LEWTHWAITE, R., 133
Leyte, 96
Leyte campaign, 125
Liberia, 455
Lichen planus, atypical, associated with Atabrine suppressive therapy, 477, 501
Life cycle, of *Phlebotomus papatasii*, 55
LINDGREN, A. J., 76
Lipiodol, 363
LIPMAN, B. L., 118
Liquor arsenicalis, 500
Liver, 519
effect of Atabrine on, 550–551
involvement of, in malaria, 483
LIVINGOOD, Maj. CLARENCE S., 281n, 305
LIVSCHITZ, J. M., 56
Lobar pneumonia, 1, 16, 17, 28
deaths due to, 243
immunity to, 31
incidence of, 21
prevalence of, 29
treatment of, 30, 32
See also Bacterial pneumonia; Pneumonia.
Lobectomy, 45
in tuberculosis, 384, 385
LÖFFLER, FRIEDERICH, 318
Löffler's medium, 275, 294
LONG, Col ESMOND R., 331, 349, 384
Longview State Hospital, 446
LORANGER, G. L., 209
Louse control, in prevention of epidemic typhus, 201
Louseborne infection. *See* Epidemic typhus.
Louseborne relapsing fever, confusion of, with typhus, 217
Lucky Strike Camp, for recovered prisoners of war, 345
See also Military installations.
Lumbar puncture, as adjuvant therapy, in meningitis, 270
Lung abscess, 45–46
Lungs:
involvement of, in epidemic typhus, 216
malignant diseases of, 48
Luzon, 67, 112, 125, 126
Lymph glands, enlargement of, in infectious mononucleosis, 39
Lymph nodes:
generalized enlargement of, in scrub typhus, 113, 115, 126, 130
local swelling of, in cutaneous diphtheria, 295
tuberculosis of, 358, 367
Lymphadenitis, cervical, 6
Lymphadenopathy, 76, 483
in scrub typhus, 111, 127
Lymphangitis, in cutaneous diphtheria, 295
Lymphatic tissue, inflammation of, 4
Lymphocytic choriomeningitis, 79, 99–101
differential diagnosis of, 100
directives on, 100, 101
incidence of, 100
Lymphocytosis, in—
dengue, 74
epidemic typhus, 217
malaria, 489
Lymphogranuloma venereum, 431–432
LYON, Dr. JOHN M., 385
Lysis, in murine typhus, 208, 221

M. & B. 693. *See* Sulfapyridine.
MACARTHUR, Gen. DOUGLAS, 466
Macedonia, 449
Machine Records Unit, Allied Force Headquarters, 508
MAHON, Col. HUGH W., 385
MAHONEY, J. F., 414, 423
MAIER, Dr. J., 136, 195

Malaise, in—
Brill's disease, 202
epidemic typhus, 143
meningococcal bacteremia, 245
poliomyelitis, 94
Q fever, 106
rheumatic fever, 231
sandfly fever, 56
scrub typhus, 111
Malaria, 7, 16, 57, 66, 68, 82, 257, 449–463, 465–477, 479–492, 493–524
admissions for, 450, 460
anemia in, 487, 490, 501, 508
attack rates for, 454, 455, 456, 457, 458
blood picture in, 489–490
breakthrough of, during suppressive treatment, 469, 475, 535, 536
case histories, 517–523
cerebral, 130, 484–485
chronic, 487–488, 496
classification of patients with, 508
clinical aspects of, 479–492
clinical attacks of, 468, 471, 480, 498
clinical types of, 504
complications of, 484–487
deaths due to, 243, 450, 460–462, 514
diagnosis of:
aids in, 482
blood studies in, 489–490
laboratory evidence in, 489–491
laboratory procedures in, 509
parasite identification in, 489
serological tests in, 490–491
differential diagnosis in, 76, 491–492
directives on, 465, 499, 500, 508, 510, 511, 540, 546
drugs used in, toxic reactions of, 501, 536, 550–558, 561, 574–576, 585–588
etiological agents of, 455
factor of, in activating tuberculosis, 360
factors predisposing to, 480
historical note, 449–451
hospitalization for, 506–509
duration of, 459, 460, 508–509
in evacuation hospitals, 506–507, 509
in general hospitals, 507–508, 509
in medical battalions, 506
in station hospitals, 508, 509
immunity to, 489
in civilian populations, 502
in India-Burma theater, 498–502
in infantry divisions, 451–452, 458
in Mediterranean theater, 502–524
Malaria—Continued
in the Pacific, 495–498
in South Pacific Area, 495–498
incidence of, 453, 503–506
during Spanish-American War, 450
during U.S. Civil War, 450
during World War I, 450
involvement of nervous system in, 485–486
lack of knowledge of, 493
morbidity, 514
mortality, 514
noneffectiveness due to, 37, 451, 495, 504
onset of, 481
quinine-Atabrine-Plasmochin treatment recommended for, 510
readmissions for, 460
reclassification of patients with, 508
relapses in, 455–459, 488–489
combined quinine-Plasmochin treatment on rate of, 579–592
statistics of, 449–463
studies of liver function in, 490–491
summary, 492
suppression of, 465–477
action of sulfamerazine in, 470, 529
by Atabrine therapy, 466–468
field experience in, 471, 546
suppressive treatment of:
effect of Atabrine withdrawal in, 468–469
factors in early failures of, 466–468
in Southwest Pacific Area, 498
symptoms of, 479, 566
clinical, 481–484
prodromal, 481
transfer diagnosis of, 507
treatment of, 452, 493–524
antimony compounds in, 528
arsenicals in, 526
Atabrine in, 465, 466–477, 510–511
bismuth compounds in, 528
chloroquine diphosphate in, 566
cinchona alkaloids in, 531–538
directives on, 499, 500, 509–510, 511
drug of choice in, 531
effectiveness of drugs used in, 500–502, 532, 536, 541, 542, 543, 548, 560, 563, 573, 574
in South Pacific Area, 495–498
introduction, 493–495
iron, 512
oxophenarsine hydrochloride in, 526
penicillin in, 525–526
plan of, 500

Malaria—Continued
treatment of—Continued
Plasmochin in, 501, 511, 579–592
quinine in, 510, 531–535
results of, 514–517
Sontochin, 559–562
Sontoquine in, 512
sulfonamides in, 512, 528–529
to reduce relapse rate, 513–514
types of, 454–455
Malaria Committee, Allied Force Headquarters, 494
Malaria transmission, areas of, 471
Malaya, 111, 493
MALLORY, Lt. Col. TRACY B., 25
Malnutrition:
factor of, in tuberculosis, 345, 392
in recovered prisoners of war, 345
Management, of—
asthma, 43
chronic bronchitis, 42–43
primary atypical pneumonia, 21
spontaneous pneumothorax, 47
venereal diseases, 425
Manchuria, 81, 86, 195
MANIFOLD, J. A., 581, 585
Manila, 93, 125, 210
Manitoba, 82, 85
Mapharsen, 419, 421, 426
in malaria, 526
MARANGONI, B. A., 255
Marches, effect of, on suppressive action of Atabrine, 470
Marianas Islands, 68, 284
Markham Valley, 112, 120
Mateur, 49
MATSON, R. C., 331
MATTHEWS, Lt. Col. EDWARD DES., 15, 24, 25
MAXCY, K. F., 204
Mazzine test, 490
MCDANIELS, H. E., 306, 321
MCDONALD, W., 59
MCGAVACK, T. H., 255
MCGUINNESS, A. C., 36n, 37
MCLESTER, Col. JAMES B., 480, 515
MEADE, Lt. Col. RICHARD H., 382
Measles, 1, 32–35, 217
complications of, 32, 34
epidemiology, 33–34
immunity to, 32
in continental United States, 34–35
in oversea theaters, 35
incidence of, 33
Measles—Continued
introduction, 32–34
susceptibility to, 32, 34
"Medical and Surgical History of the War of the Rebellion," 329
Medical battalions:
in chain of evacuation, 506
management of malaria in, 506
Medical causes, for evacuation:
asthma, 44
malaria, 517
Medical circular letters, pertaining to diphtheria, 279
See also Directives, pertaining to diphtheria.
Medical Consultants Division, Office of the Surgeon General, 553
Tropical Disease Treatment Branch of, 283
Medical Department Professional Service Schools, 138, 437, 444
Division of Virus and Rickettsial Diseases of, 179, 180
Medical General Laboratory:
1st, 138
15th, 8, 25, 104, 105
19th, 96
Medical Laboratory:
2d, 104
3d, 119
4th, 302
6th, 359
7th, 302
Medical Research and Development Board, U.S. Army, 380, 384
Medical shock, complicating malaria, 486
Medical Statistics Division, Office of the Surgeon General, 2, 395
Mediterranean Sea, 52, 53
Mediterranean theater, 9, 99, 125, 279, 453, 455, 458, 459, 479
bacterial pneumonia in, 32
consultant in medicine in, 8
common respiratory infections in, 7
diphtheria in, 276
evacuation policy in, 507
fever of undetermined origin in, 53–55
influenza in, 15–16
malaria in, 453, 502–524
Atabrine for suppression of, 494–495
evacuation for, 516
hospitalization for, 506–509
incidence of, 503–506

Mediterranean theater—Continued
malaria in—Continued
treatment of, 502, 509–512
measles in, 35
mumps in, 38
primary atypical pneumonia in, 23–25
Q fever in, 103
rheumatic fever in, 229
sandfly fever in, 49, 51, 53–55
streptococcal infections in, 7
tuberculosis in, 353–357
admission rates for, 353–354
care of patients with, 359
disposition of patients with, 355–356
epidemiology of, 356–357
evacuation of patients with, 357
hospitalization for, 354–355, 359
special problems related to, 359–360
therapy, 355–356
Melbourne, 360
MELENEY, Dr. HENRY E., 493
MELNICK, J. L., 447
Membranes, serous, tuberculosis of, 367
Meninges:
reactions in, in epidemic and scrub typhus, 170
tuberculosis of, 358
Meningismus:
in cerebral malaria, 485
in *falciparum* malaria, 481, 484
Meningitis, 491
case histories, 247, 248
cerebrospinal fluid in, 266
complications of, 258–259
deaths due to, 7
differential diagnosis of, 76
duration of life with, 257, 258
epidemics of, 239
in European theater, 241
meningococcal, 239, 256–258
antiserum in, 239
complications of, 258–259
confused with typhus, 217
mortality in, 262
myocarditis in, 258
pathological findings in, 270–271
resemblance of cerebral malaria to, 485
sequelae of, 258
treatment of, 272–273
adjuvant therapy in, 269–270
antitoxin, 265–266
serum in, 265
sulfonamides in, 262, 273
tuberculous, 100, 367
Meningococcal antitoxin, in treatment of meningitis, 265–266
Meningococcal bacteremia, 244–249
cutaneous manifestations of, 245
onset, 245
rash in, 245–246
symptoms of, 244–245
transition from, to meningitis, 248–249
variations in, 246–248
See also Fulminant meningococcal bacteremia.
Meningococcal infections, 239–273
carriers of, 244
case history, 256
complications of, 258–259
conjunctivitis in, 260
death due to, 242, 243, 252
cause of, 252
diagnosis of:
clinical, 261
laboratory, 260–261
directives on, 242, 261, 266, 269
discussion of, 273
epidemic of, 241
historical note, 239–240
incidence of, 241–244
mortality for, 243
pathogenesis, 244
pneumonia in, 259
treatment of, 261–270, 271–272
antibiotics in, 266–269
sulfonamides in, 239, 240, 242, 271, 272
Waterhouse-Friderichsen syndrome in, 249, 251, 252, 253n
Meningococcal meningitis. *See* Meningitis.
Meningococcemia, 217, 244–249
case histories, 246, 247, 249, 250, 251
forms of, 246–247
rash in, 245–246
symptoms of, 244–245
temperature in, 246
treatment of, 262
variations in, 246–247
Meningococci, types of, 260, 261
Mental confusion, in Japanese B encephalitis, 88
Merano, 283, 315
Meta-aminobenzoic acid, 196
Metabolic studies, in epidemic typhus, 152–153
Methods, for reduction of airborne infection, 6
Mexico, 143
MEYER, Dr. KARL F., 80

Micro-organisms, of common upper respiratory infection, 2, 4, 7, 17, 26, 33
Microtus montebelli, 111
Middle East, 94, 99, 297, 454, 460, 488
  sandfly fever in, 56
Middle East theater, 102
  rheumatic fever in, 229
  tuberculosis in, 366
Middle Pacific Area, tuberculosis in, 364
  diagnosis of, 364
  evacuation for, 364
  incidence of, 364
MIDDLETON, Col. WILLIAM S., 293, 321
Miliary tuberculosis, 358, 367
Military campaigns, effect of malaria in, 449–450
Military discharges. *See* Disability separations.
Military government, in Germany:
  Public Health Branch of, 398
  tuberculosis control program of, 397–399
Military Government Research Center, 87
Military importance, of—
  dengue, 59, 70, 76
  lymphocytic choriomeningitis, 101
  sandfly fever, 49
  seasoning of troops, 5, 7, 23
Military installations:
  Camp Adair, 36
  Camp Bullis, 441
  Camp Claiborne, 19
  Camp Dix, 33
  Camp Forrest, 394
  Camp Lee, 28
  Camp Lucky Strike, 345
  Camp McCoy, 37
  Camp Patrick Henry, 106, 107
  Camp Pike, 33
  Fort Belvoir, 44
  Fort Benning, 597
  Fort Bragg, 6, 12, 19, 105, 108, 267, 384, 417, 421, 437
  Fort Eustis, 44
  Fort Knox, 226, 545, 597
  Fort McClellan, 97
  Fort Sam Houston, 96, 97
  Fort Sill, 34
  Fort Francis E. Warren, 226
Military Mission of U.S.S.R., in Great Britain, 349
Military service, tuberculosis detected before induction into, 331–333
Military significance, of Q fever, 109
Military units:
  Airborne Infantry, 88th, 443
  Field Artillery, 77th, 165
  Infantry Division:
    25th, 279, 307, 313, 317, 452, 458, 497
    27th, 279, 280, 297, 304, 313
    32d, 121, 452
    36th, 50
    37th, 458
    41st, 122
    43d, 279, 313, 317, 452, 458
  Infantry Regiment:
    35th (25th Division), 307
    147th, 496, 497
    164th (Americal Division), 280
    186th, 122
    339th, 104
    362d, 104
  Parachute Infantry Regiment, 503d, 120
Milk:
  directives on purchase of, 368
  unpasteurized, factor of, in nonpulmonary tuberculosis, 367, 368
Milkborne streptococcal infection, 8, 17, 28
MILLER, Lt. L. M., 86
Milne Bay, 112
Mindanao, 210
Mindoro, 112, 125, 126
Ministry of Health, England, 15
Ministry of Public Health, Egyptian Government, 145–146, 157
Mite ulcer, of scrub typhus, 130
Mobile X-ray Team No. 3, 341
Mobilization Regulations No. 1–9, 238, 340
Mode of transmission, of—
  acute respiratory diseases, 1
  dengue, 59
  epidemic typhus, 143
  murine typhus, 204
  Q fever, 108–109
Moist heat, in treatment of poliomyelitis, 98
Monilia, 280
Mononucleosis, infectious, 38–41, 100, 489
  age in, 39
  antibodies in, 40
  cephalin flocculation reaction in, 39
  classical form, 39
  communicability of, 39
  differential diagnosis of, 76
  epidemics of, 40
  in continental United States, 40–41
  in oversea theaters, 41
  introduction, 38–40

Mononucleosis, infectious—Continued
serological reactions in, 40
sex in, 38
MOORE, Dr. JOSEPH E., 416, 424, 426
Moore General Hospital, 387–388
census of tuberculous patients in, 387
designation of, as specialty center for tuberculosis, 382, 387
transfer of, to Veterans' Administration, 388
See also Hospitals, general.
MOOSER, H., 204
MORAGUES, V., 195
Morale, 390
factor of, in scrub typhus, 137
Morocco, 210, 453, 502
Morphine, 76
use of, in meningitis, 270
Morphology, of diphtheritic lesions, 284–288
Mortality. *See* Death(s).
MOSHER, W. E., Jr., 87
Mosquito control, for prevention of dengue, 60, 61, 63, 64, 66, 67, 69, 71
Mouse-brain formalin (inactivated) vaccine, in Japanese B encephalitis, 90
Mouse neutralization test, in typhus fever, 190
MTOUSA (Mediterranean Theater of Operations, U.S. Army). *See* Mediterranean theater.
MUCKENFUSS, Col. RALPH S., 21, 81
Mucous membranes, effect of Atabrine on, 552–553
MUIR, E. G., 297, 312
Mumps, 35–38
complications of, 35–37
epidemics of, 37
in continental United States, 37–38
in oversea theaters, 38
introduction, 35
meningoencephalitis, 100
noneffectiveness due to, 36
occurrence of, 37
quarantine for, 38
Munda, 451
Murine typhus, 204–215, 252, 257
case histories, 212
causative agent of, 204, 205
clinical description of, 204
clinical experience with, 205–213
clinical findings in, 208
diagnosis of, laboratory aids in, 213–215
epidemiology of, 204–205
Murine typhus—Continued
foci of, 205
incidence of, 205, 207, 208
incubation period of, 221
laboratory findings in, 208
mode of transmission of, 204
serological findings in, 211, 213, 214
summary, 221–223
clinical picture, 221–222
diagnosis, 222
immunity, 222
natural course, 222
prophylaxis, 223
therapy, 223
vector of, 205
MURRAY, E. S., 136, 197
MURRAY, R., 280
Muscle pain, in relapsing *vivax* malaria, 487
Muscles, aching of, in meningococcal bacteremia, 245
Muscular aches, in Q fever, 106
Muscular weakness, in murine typhus, 221
Musculoskeletal system:
defects of, disability discharge for, 339
symptoms referable to, complicating malaria, 487
Mustard gas, as cause of chronic bronchitis, 43
Mycobacterium tuberculosis, 32
MYERS, Lt. Col. DANIEL W., 15, 24, 25
Myitkyina, 128, 136, 281
Myocardial damage, associated with scrub typhus, 124
Myocarditis, 259
complicating cutaneous diphtheria, 295
following scrub typhus, 125
in diphtheria, 321
death due to, 302
in meningitis, 258
Myocardium, involvement of, in epidemic typhus, 216

Nadzab, 120, 122, 123
Naples, 8, 103, 104, 107, 220, 354, 502, 506
epidemic typhus in, 154
Nasopharyngeal diphtheria. *See* Diphtheria.
Nasopharyngitis, 2
Nasopharynx, autoinfection of, from skin, 298
National Guard, federalization of, 241, 330
National Institute for Medical Research, 138

National Institute(s) of Health, U.S. Public Health Service, 108, 135, 179, 190, 444, 594
National Research Council, 30, 47, 228, 409, 412, 538
Committee on Medical Research of, 525
Committee on Medicine of, 420
Division of Medical Sciences of, 94, 136, 171, 493
Subcommittee on Tropical Diseases of, 493
Subcommittee on Tuberculosis of, 374, 384
Subcommittee on Venereal Diseases of, 409, 419, 420, 423, 424, 425, 426
National Tuberculosis Association, 389, 406
Nausea, in—
cutaneous diphtheria, 303
dengue, 72
malaria, 483
meningococcal infections, 245, 253
pancreatitis, 36
sandfly fever, 56
suppressive malaria therapy, 466, 495, 536, 556
Naval Medical Research Unit No. 2, 86, 90
Nazi Party, 349
Negro troops:
blackwater fever in, 486
mumps in, 38
toxic reactions to Plasmochin, 501
Negros, 126
NEILL, 204
Neisseria intracellularis, 258, 259
Neoarsphenamine, 500
in malaria, 526
in syphilis, 418
Nephritis, 1
hemorrhagic, 75
Nervous system, involvement of, in malaria, 485–486
Nervousness, in relapsing *vivax* malaria, 487
Netherlands, diphtheria in civilian populations in, 316
Netherlands East Indies, 282
Netherlands New Guinea, 112, 121, 125
Neurasthenia, during convalescence from dengue, 75
Neuritides, associated with malaria, 486
Neuritis:
complicating cutaneous diphtheria, 288, 295
diphtheritic, 299–302
incubation period of, 301
Neurocirculatory asthenia, 125
complicating malaria, 487
following rheumatic fever, 234
Neurological disease, disability discharge due to, 339
Neurological involvement, degree of, in epidemic typhus, 146
Neurosyphilis, 427–428
treatment of, 428
Neurotropic virus, diseases due to, 79–102
Neutralization test. *See* Test(s).
Neutropenia, in epidemic typhus, 217
"New and Nonofficial Remedies," 266
New Britain, 112, 120
New Caledonia, 359, 360, 451–452
outbreak [illegible] 63
New Geo[illegible]
New Guinea, [illegible], 112, 120, 122, 123, 282, 451, 452, 469–470, 498
outbreak of dengue in, 65–68
New Hebrides, 279, 284, 298, 304
outbreak of dengue in, 62–63
New World, 143
New York Port of Embarkation, 378
New York State Department of Health, 315
New Zealand, 95, 279, 317, 318, 359, 452, 497
NICOLLE, 143
Nitrogen balance, in typhus fever, 153
Nitrogen retention, in epidemic typhus, 146
Noneffectiveness, due to—
common upper respiratory infections, 5–6
cutaneous diphtheria, 307–308
dengue, 65
dermatophytosis, 37
malaria, 451
measles, 34
mumps, 36–37
rubella, 42
sandfly fever, 49
spontaneous pneumothorax, 47
Nonhemolytic streptococcus, 19
Nonimmune military personnel, 67
factor of, in dengue epidemics, 59
suppression of malaria in, 535
Nonparalytic poliomyelitis, 93, 96, 97, 100
See also Poliomyelitis.
Nonpulmonary tuberculosis, incidence of, 369
Nonspecific urethritis, 418
Nordhausen concentration camp, 349
Normandy, 393
NORRIS, R. F., 280, 482, 483n

North Africa, 49, 53, 94, 97, 102, 104, 143, 284, 451, 559
North African campaign, 275
North African Theater of Operations, U.S. Army. *See* Mediterranean theater.
Northern Hemisphere, 10
Norway, diphtheria in civilian populations in, 316
Nottinghamshire, 38
Nova Scotia, 240
Nurses, tuberculosis in, 342–343
Nursing care, in epidemic typhus, 192
Nutrition, factor of, in tuberculosis, 359–360
NUTTALL, G. H. R., 318

Occupational therapy, in care of tuberculous patients, 390
Occurrence, of—
  mumps, 37
  primary atypical pneumonia, 19
  Q fever, 103–106
OCHS, L., Jr., 262, 263, 269
Ocular conditions, complicating malaria, 486
Office of Scientific Research and Development, 494, 525, 594
Office of the Air Surgeon, 227, 379
Office of the Chief Surgeon, European theater, 422, 425
  Preventive Medicine Division of, 410
Office of the Provost Marshal General, 394
Office of the Surgeon, South Pacific Area, 496
Office of the Surgeon General, 93, 346, 349, 350, 357, 365, 378, 379, 380, 387, 389, 391, 414, 419, 583
  Consultant in Tuberculosis in, 398, 406
  subordinate elements of:
    Medical Consultants Division, 283, 553
    Medical Statistics Division, 2, 395
    Preventive Medicine Service, 80, 410, 424
    Professional Service Division, 2, 9, 12, 30, 410
Officers' Training Center, Army Ground Forces, 341
Okinawa, 76
  outbreak of Japanese B encephalitis on, 86–89
Old World typhus. *See* Epidemic typhus.
Oliguria:
  in epidemic typhus, 146
  in meningococcemia, 263, 269
OPIE, Maj. EUGENE L., 368
OPPEL, T. W., 282n, 298, 304
Optic nerve:
  atrophy of, in meningitis, 259
  blanching of, in malaria, 485
Oran, 50
Orchidotomy, 37
Orchitis, 37, 38, 76
  surgical decompression for, 36
Organisms, of common upper respiratory infections, 3, 4, 7, 39
Orient, 343
Orientation, of tuberculous patients, 388–390
Orlando Army Air Base, 233
Oro Bay, 116, 124
Ortho-aminobenzoic acid, 196
OSIPOV, Col. B. A., 349
Osteoperiostitis, in meningitis, 259
Otitis, 15
Otitis media:
  complicating measles, 32, 34
  complicating typhus, 147, 222
  in respiratory infections, 9
OTTO I, 449
Outbreaks. *See* Epidemic(s).
OWEN, Lt. Col. GEORGE C., 386
Owen Stanley Range, 113
Owi, 125
  outbreak of scrub typhus on, 121–123
Oxford University, 550
Oxophenarsine hydrochloride, 419
  in treatment of malaria, 526
Oxychloroquine, 577–578
  absorption, 577
  antimalarial activity of, 577
  clinical testing of, 577–578
  dosage of, 577
  general properties of, 577
  in *falciparum* malaria, 577
  in *vivax* malaria, 577
  plasma levels of, 577
  toxicity of, 577
Oxytetracycline, effectiveness of, in—
  bacteremia, 269
  meningitis, 269, 273
  Q fever, 109
  scrub typhus, 139

PABA. *See* Para-aminobenzoic acid.
Pachymeningitis, 252, 257
Pacific, 275
Pacific areas, 8
  influenza in, 16
  See also South Pacific Area; Southwest Pacific Area.

Pacific Ocean Area:
dengue in, 69
tuberculosis in, 358
in recovered prisoners of war, 391
PADDOCK, Maj. FRANKLIN K., 511
Paestum, 453, 502
Pagliana, 24
Pain, 76
in back:
in malaria, 481
in murine typhus, 221
in poliomyelitis, 94, 97
in chest, in Q fever, 107
in joints, in meningococcal infections, 245, 253
in shoulder, in rabies, 101
retro-orbital, 56
Palate, discoloration of, factor of Atabrine in, 553
Palermo, 165
Palestine, 275, 284, 318
Palpitation, in relapsing *vivax* malaria, 487
Pamaquine naphthoate, 498
clinical experience with, 585–588
historical review, 579–582
studies of:
at a specialty center, 582–585
materials for, 583
methods of, 583
prewar, 580–581
results, 583–585
summary, 582, 592
wartime, 581–582
therapeutic use of, 588–589
toxicity of, 585–589
See also Plasmochin naphthoate.
Panama, 42, 76, 101, 103, 106, 108, 451, 491, 535, 582, 587
Pancreatitis, complicating mumps, 36
Pandemic influenza, 10, 11, 16, 17
See also Influenza.
PANJA, G., 292
Pappataci fever, 506
See also Sandfly fever.
Papua, 112, 116, 120, 122, 125
Para-aminobenzoic acid, 136
in murine typhus, 223
regimen of treatment of, 199
study of, on growth of typhus rickettsiae, 195–200
use of, in epidemic typhus, 155
Parachute infantry regiment, scrub typhus in, 120
See also Military units.
Paraldehyde, 102, 192
in meningitis, 270
Paralytic poliomyelitis, 93, 97
See also Poliomyelitis.
Parasite factor, in precipitation of malarial paroxysm, 480
Parasite identification, in malaria, 489, 509
Parasite species, of malaria, effect of suppressive therapy on, 469–470
Parasitemia, 529
control of:
with chloroquine diphosphate, 565
with quinine, 510, 532–533
effect of penicillin on, 526
effect of sulfonamides on, 529
of *falciparum* malaria, 529
of *vivax* malaria, 529
action of arsenicals upon, 526
Parasitological studies, of diphtheria, 280
Paresis, residual, of cerebral malaria, 485
Paris, 138, 302
Parotid glands, 35
Parotitis, complicating typhus, 147, 220, 222
Paroxysm, malarial, 490, 491
action of arsenicals upon, 526
action of bismuth compounds upon, 528
factors in precipitation of, 480
Pasadena College, 97
PASRICHA, C. L., 292
Pasteur Institute, 105, 210
Pathogenesis, of meningococcal infections, 244
Pathogenicity, of *Corynebacterium hemolyticum*, 320
Pathological findings, of meningitis, 270–271
Pathology:
of epidemic typhus, 169–172
of scrub typhus, 132–133
Patients:
disposition of, 123–125, 233, 236–237, 341–342, 355–356
duration of hospitalization for, 459, 509
early ambulation of, 233
evacuation of, to Zone of Interior, 98, 132, 360, 361, 362, 363, 364, 378–381
orientation of, 388–390
quarantine of, for mumps, 38
reclassification of, 508
reconditioning of, 235
rehabilitation of, 388–390
Patrol activity, factor of, in diphtheritic lesions, 286
PAUL, Dr. JOHN R., 52, 56, 57, 443, 447
PAULLIN, 204

PECK, J. L., 86
Pediculus humanus var. *corporis*, 143
PELOUZE, Dr. P. S., 412
Penicillin, 30, 32, 414–418
  fractions of, 426
  in common upper respiratory infections, 9
  in cutaneous diphtheria, 289, 305–306
  in diphtheria, 321–325
  in epidemic typhus, 194, 195
  in malaria, 525–526
  in meningococcal infections, 266–269
  in scrub typhus, 136
  in syphilis, 423–427
Penicillium chrysogenum Q–176, 426
Penicillium notatum, 426
Peninsular Base Section, 507
Pentaquine, 592, 594
Pericarditis:
  death due to, 225
  in meningitis, 259
Peripheral edema, 272
Peripheral neuritis:
  complicating scrub typhus, 119
  in malaria, 485
Peripheral vascular failure, in typhus fever, 220
Peritonsillar cellulitis, 4, 7
PERKINS, R. F., 299n, 300
Perspiration, profuse, in malaria, 482
Peru, 571, 572, 574
Pescadores Islands, 111
PESQUERA, Lt. Col. GILBERTO S., 398
PETERS, M., 262n, 263
Pfeiffer's bacillus, 10
Pharyngeal diphtheria, 275, 297, 299
Pharyngitis, 8
  exudative, 4
  nonstreptococcal exudative, 7
Pharynx, 2
Phases, of Waterhouse-Friderichsen syndrome, 255
Phenobarbital, 76
PHILIP, Lt. Col. CORNELIUS B., 52, 56, 57, 208n, 443
Philippine Islands, 93, 95, 96, 99, 101, 112, 282, 391, 451, 553, 574
  chancroid in, 431
  dengue in, 65–68
  murine typhus in, 208
  scrub typhus in, 125–126
Phlebotomus, 53
Phlebotomus fever. *See* Sandfly fever.
Phlebotomus papatasii, 49, 50, 52, 53
  life cycle of, 55
Photophobia, 76
  in sandfly fever, 56
Physical activity, effect of, on suppressive action of Atabrine, 470
Physical examination, for military service:
  at induction, 45
  detection of tuberculosis by, 331
Physical findings, in Q fever, 107
Physical signs, of dengue, 74–75
PIATT, A. D., 350
PINCOFFS, Col. MAURICE C., 469, 498
PINKERTON, H., 125, 194, 195
Pisa, 393
Plasma:
  concentrations of Atabrine in, 510, 539, 540
  concentrations of quinine in, 532
  infusions of, in treatment of malaria, 512
Plasma levels, of—
  chloroquine diphosphate, 563, 568, 573
  cinchonidine, 537
  cinchonine, 537
  oxychloroquine, 577
  quinacrine hydrochloride, 539, 540, 541, 542, 543, 544, 545, 549, 557
  quinine, 532, 537
  Sontochin, 559, 561
Plasmochin naphthoate, 498, 511, 559, 579–592
  combined with quinacrine hydrochloride, 582
  combined with quinine, 580, 581, 582, 583, 585
    clinical use of, 590
    discussion of, 589–591
  gametocytes of *P. falciparum* eradicated by, 579
  historical review, 579–582
  prewar studies on, 580–581
  recommendations for therapeutic use, 588
  summary, 592
  toxicity of, 501, 585–589
  wartime studies on, 581–582
Plasmodium cynomolgi, 596
Plasmodium falciparum, 454, 455, 460, 481, 526, 529
  effect of Atabrine on, 469, 470, 496
  gametocytes of, 476
  in cerebral malaria, 499
Plasmodium malariae, 454, 455, 461, 526
Plasmodium vivax, 454, 455, 460, 468, 470, 479, 482, 488, 526, 529
  effect of Atabrine on, 496

Plasmodium vivax—Continued
gametocytes of, 476
strains of:
McCoy, 526
New Guinea, 488
relapsing tendency of, 470, 488
Pleura, tuberculosis of, 369
Pleural effusion:
complicating scrub typhus, 119
primary, 354, 356
Pleurisy, tuberculous, 342, 356
Pleurisy with effusion, tuberculous, 370–372
coding of, 370
directive on, 370
prognosis in, 371, 372
symptoms of, 371
PLOTZ, Col. HARRY, 138, 179n, 183, 184, 188, 190, 194, 195, 203, 208, 210, 214
Pneumococci, 3, 8, 10, 13
in common upper respiratory infection, 7
typing of, 29, 31
Pneumonia, 1, 8
admissions for, 26, 27
antibiotics in treatment of, 27
as differential diagnosis with malaria, 491
bacterial, 220, 222
classification of, 16
clinical concept of, 17
complicating measles, 32, 33
factor of, in activating malaria, 480
hemolytic streptococcal, 31
influenzal, 13, 15, 17
mortality for, 26
noneffectiveness due to, 37
primary, 28, 29
primary atypical, 16–19, 57, 259
admissions for, 20–21, 23, 27
characteristics of, 17, 19
clinical recognition of, 20
incidence of, 20
incubation period of, 24
mortality in, 26
studies on etiology of, 18–19
reporting of, 28, 29
secondary, 28
staphylococcal, 11
viral, 76
Pneumonitis, 108
in bronchiectasis, 45
in infectious mononucleosis, 40
in influenza, 13
in scrub typhus, 130
Pneumoperitoneum, in tuberculosis, 383, 385
Pneumothorax:
in tuberculosis, 342, 355–356, 379
spontaneous, 46–47, 373
tension, 46, 47
Poland, 143
Policy, on problem of diphtheria, 283
Poliomyelitis, 79, 91–99
age, as factor in susceptibility to, 92
deaths due to, 243
diagnosis of, 94, 97–98
epidemics of, 93, 96–97
epidemiology, 95
immunity to, 93, 95
in continental United States, 96–97
in oversea theaters, 94–96
incidence of, 91, 96
morale problem of, 97
onset of, 94
symptoms, 97
treatment, 98–99
Polyneuritis, in German prisoners of war, 283
Polysaccharides, in immunization against lobar pneumonia, 30
POND, H. S., 128
Pontine Marshes, 453, 502
Port Lyautey, 453, 502
Port Moresby, 112, 116, 118, 119
PORTEOUS, W. M., 94
Postvaccinal encephalitis:
admissions for, 84
deaths due to, 85
See also Encephalitis.
Postwar studies, on scrub typhus, 138–139
See also Clinical research.
President ROOSEVELT, 144
Prevalence:
of nonpulmonary tuberculosis, 367
of poliomyelitis, 91–92
Prevention, of malaria, penicillin in, 526
Preventive measures:
for sandfly fever, 57
for scrub typhus, 122
Preventive Medicine Division, Office of the Chief Surgeon, European theater, 410
Preventive Medicine Division, Office of the Surgeon General, 80
Preventive Medicine Service, Office of the Surgeon General, 410, 424
Venereal Disease Control Division of, 429
PRICE, A. H., 266
Primary atypical pneumonia, 16–26, 57, 103, 259
admissions for, 20–21, 23, 27

Primary atypical pneumonia—Continued
age in, 17
agglutinins in, 19, 22, 24, 25
British recognition of, 22
cold agglutinin tests for, 22, 24
communicability of, 20, 24
convalescence, 21
course, 17, 19, 21
deaths due to, 21, 243
differential diagnosis, 362
etiology of, 18
in continental United States, 19–21
in oversea theaters, 21–26
incidence of, 20
incubation period, 24
introduction, 16–19
management of, 21
occurrence of, 19
onset, 17
pleural effusions in, 21
recognition of, 18, 22
reporting of, 20, 23
residual of, 26
serological reactions in, 18–19
summary, 25–26
See also Pneumonia.
Primary pleural effusion, 354
PRINZING, F., 449
Prisoner-of-War General Hospital No. 2, Camp Forrest, 394, 395
Prisoners of war. *See* Captured prisoners of war.
Prodromal symptoms:
of malaria, 481
of meningococcal bacteremia, 244–245
Professional Service Division, Office of the Surgeon General, 2, 9, 12, 30, 410
Prognostic sign, of scrub typhus, 131
Promin, 382
Promizole, 382
Prophylaxis, against epidemic typhus, 201
Prostration, associated with epidemic typhus, 146
Proteins, serum content of:
in epidemic typhus, 217
in typhus fever, 153
Proteus, strains of:
Kingsbury (K), 133
OX-K, 112, 113, 115, 119, 125, 126, 127, 139, 179
OX-2, 179
OX-19, 127, 133, 179
"Pseudobronchiectasis," 45
Psittacosis, as type of virus pneumonia, 17
Psittacosis virus, 22
Psychoneurosis, disability discharge due to, 339
Psychosis, 257
Atabrine as factor in, 556–557
disability discharge due to, 339
in suppressive malaria therapy, 477
residual of cerebral malaria, 485
Public Health Branch, Military Government for Germany (United States), Preventive Medicine Branch of, 398
Public Law 16, 78th Cong., 390
Public Law 346, 78th Cong., 390
Puerto Rico, 366, 451
Pulmonary edema, in bacteremia, 271, 272
Pulmonary emphysema, 48
Pulmonary fibrosis, 47–48
Pulmonary infarction, complicating scrub typhus, 119
Pulmonary tuberculosis, 358
See also Tuberculosis.
Pulse, elevated, in cutaneous diphtheria, 295
Purpura hemorrhagica, 252
Purulent complications, of common cold, 3–4
Pyrimethamine, 597, 598

Q fever, 25, 103–109
antibodies, 104, 105, 106
clinical features of, 106–108
convalescence, 107–108
course of, 107–108
cross-immunity in, 108
differential diagnosis, 104
dust associated with, 105, 108, 109
epidemics of, 105–106
in Apennines, 103–105
in Greece, 105–106
in Zone of Interior, 106
epidemiology, 108–109
incidence of, 104
incubation period in, 104–105
laboratory findings, 108
laboratory outbreaks of, 105
military significance of, 109
mode of onset, 106
mode of transmission, 108–109
occurrence, 103–106
physical findings, 107
recognition of, 103
rickettsia of, 104, 105, 108
roentgenological findings, 107

Q fever—Continued
symptoms, 106–107
treatment, 108
Quarantine, for mumps, 38
Quartan malaria, 489
Queensland, 60, 103, 111, 112
QUILLINAN, 300
Quinacrine hydrochloride, 115, 452, 465, 538–558
aplastic anemia ascribable to, 551–552
as cortical stimulant, 558
clinical trial of, 538–558
dosage schedule, 538, 540, 545–549
hepatic dysfunction related to, 550–551
in acute attacks, 540–542
in *falciparum* malaria, 534, 539, 540, 542–545
in relapsing malaria, 534
in suppression, 545–549
in *vivax* malaria, 539–540
relative efficiency of, 569
physiological disposition of, in human body, 539
plasma concentrations of, 540
levels of, 540, 541
reactions, acute, to short-term administration of, 555–559
central nervous system, 556–558
gastrointestinal tract, 556
skin, 556
skin discoloration associated with, 552
studies on, 538–558
clinical use, 540–549
general properties, 539–540
summary, 558
toxicity, 550–558
superiority of, to quinine, 532, 533, 534
toxic manifestations of, 534, 550–558
See also Atabrine.
Quinine, 115, 511–512, 525, 529, 583
clinical trial of, 531–535
combined with Plasmochin, 580, 581, 582, 583, 585
dosage of, 532
in *falciparum* malaria, 532, 534
in relapsing malaria, 534
in *vivax* malaria, 532
relative efficiency of, 569
in treatment of malaria, 466, 531–535
inferiority of, to Atabrine, 470
intramuscular injections of, 535
intravenous injections of, 500, 501, 512, 534
Quinine—Continued
malaria suppression by, effect of combat conditions on, 466
oral administration of, 511
plasma concentrations of, 532
level of, 532
source of, 493
toxicity of, 501, 534

Rabat, 453, 502
Rabies, 79, 100, 101–102
deaths due to, 101
incubation period, 101
symptoms, 101–102
Race, factor of, in tuberculosis, 367, 375
RAMMELKAMP, C. H., 266
RAMP's. *See* Recovered Allied military personnel.
Randolph Field, 235
See also Army airfields.
Rash, in—
Brill's disease, 202
dengue, 72
epidemic typhus, 216, 217
Fort Bragg fever, 438
meningococcal bacteremia, 245–246, 249
murine typhus, 221, 222
RASMUSSEN, AARON F., Jr., 99n, 100
Reaction(s):
cephalin flocculation, in mononucleosis, 39
Pandy, in Japanese B encephalitis, 89
serological, in primary atypical pneumonia, 18–19
toxic, to—
Atabrine, 495, 550–558
chloroquine diphosphate, 574–576
oxychloroquine, 577
pamaquine, 585–589
quinine, 501, 534
Sontochin, 561
Weil-Felix, 40
in epidemic typhus, 157, 179–183
in Fort Bragg fever, 441
in Q fever, 103, 104
in infectious mononucleosis, 40
in scrub typhus, 119, 125, 133–134
in typhus, 157, 181, 182
Proteus OX-K in, 125, 126, 127, 128, 133–134, 179–183
Proteus OX-19 in, 133, 179, 180, 181, 183, 208, 213
Proteus OX-2 in, 179, 180, 183
REAGAN, R. L., 138

Reconditioning:
after rheumatic fever, 235
for scrub typhus convalescents, 124
for tuberculous patients, 388–390
Recovered Allied military personnel, tuberculosis in, 346–349
Recovered American prisoners of war, tuberculosis in, 344–346
Recovered prisoners of war, tuberculosis in, 390–392
Recruits:
incidence of common respiratory diseases related to proportion of, 5
incidence of measles in, 33
Red Cross, 344, 389
canteens of, 368
Redistribution Station, Army Ground Forces, 346
Reflexes, in Japanese B encephalitis, 88
Regiments. *See* Military units.
Registrants, for military service:
rejection of, for venereal disease, 433
screening of, 333
Rehabilitation:
after primary atypical pneumonia, 22
of tuberculous patients, in Zone of Interior hospitals, 388–390
REILLY, Col. WILLIAM A., 165
Rejection, for military service, due to tuberculosis, 331
Relapsing malaria:
causative agent of, 469
morbidity of, 514–517
treatment to reduce rate of, 513–514
See also Malaria.
Renal complications, of sulfonamide therapy, in meningitis, 262–263
Report(s):
essential technical medical data, 51, 500
statistical health, 28, 50, 51, 96
summary health, 28
Reporting—
of pneumonia, 20, 23, 28, 29
of tuberculosis, 406
Research:
in rheumatic fever, 238
on dengue, 76–78
Reservoir host:
of epidemic typhus, 143
of scrub typhus, 111
Residual, of scrub typhus, 124
Respiratory aids, in poliomyelitis, 98
Respiratory tract, diseases, 1–48
acute, 2–42
bacterial pneumonia, 26–32
common upper respiratory infection, 2–9
infectious mononucleosis, 38–41
influenza, 9–16
measles, 32–35
mumps, 35–38
primary atypical pneumonia, 16–26
rubella, 41–42
chronic, 42–48
chronic bronchitis, 42–44
bronchiectasis, 44–45
lung abscess, 45–46
malignant disease of lungs, 48
pulmonary emphysema, 48
pulmonary fibrosis, 47–48
spontaneous pneumothorax, 46–47
disability discharge due to, 339
general considerations, 1–2
in malaria, 483–484
See also specific diagnosis.
Restlessness:
in dengue, 72, 76
in meningitis, 270
Retinopathy, in scrub typhus, 130
REYNOLDS, F. H. K., 59
Rheumatic disease, 1
Rheumatic fever, 225–238, 247
acute, 231
arthralgia in, 235
carditis in, 231
clinical investigation of, 238
clinical picture of, 229–231
complications of, 234–235
control programs for, 237–238
death due to, 231, 232
directives on, 227, 232, 233, 236. *See also* Directives.
disposition of patients with, 233, 236–237
epidemics of, 227
epidemiology of, 228–229
in oversea theaters, 229
in young adults, recovery from, 234
incidence of, 226, 228
information on, clinical and historical, 230
military importance of, 225
natural history of, 229
outbreaks of scarlet fever following, 226
reconditioning during convalescence from, 235
statistics, 228–229
sulfonamide prophylaxis for, 227, 228

Rheumatic fever—Continued
summary, 238
treatment of,
directive on, 232
early, 232–233
late, 233–235
results of, 233–235
Rheumatic fever convalescent centers, hospitals designated as, 233
Rheumatism, death due to, 225
Rhine, 343
Rhineland, 166
Rhinitis, fibrinous, 297
RICH, A. R., 47, 250
Rickettsia burneti, strains of:
"Balkan grippe," 105, 106, 108
Henzerling, 104, 105, 108
Paige, 104, 105
Seale, 105
Rickettsia mooseri, 189, 204, 205, 212
Rickettsia prowazeki, 143, 195, 202
strains of:
Breinl, 156
identification of, 190–192
isolation of, 190–192
Rickettsia tsutsugamushi, 111, 112, 123, 135, 136, 137, 138
Rickettsiae, of—
epidemic typhus, 143
murine typhus, 205
Q fever, 104, 105, 108
scrub typhus, 111
Rickettsial agglutination, in epidemic typhus, 188–189
Rickettsial infections, antibiotics in treatment of, 139
RIGHTS, F. L., 138
RITTMAN, G. E., 417
ROBBINS, Maj. FREDERICK C., 103, 104, 105
Rockefeller Institute of Medical Research, 81, 239
Rockhampton, 61
Rocky Mountain spotted fever, 190, 252
Roentgenographic examination:
at induction, 2, 45, 331
tuberculosis detected by, 334
Roentgenological findings, in Q fever, 107
ROLLESTON, J. D., 318
ROMANSKY, M. J., 417
Rome, 105, 502
ROOSEVELT, THEODORE, 450
ROPER, Maj. WILLIAM H., 384, 391
ROSENBERG, A. A., 490
ROSENBERG, Dr. D. H., 266
Royal Air Force, tuberculosis in, 402–403
Royal Navy, tuberculosis in, 400–402
ROYSTER, H. P., 306
Rubella, 41–42
communicability of, 41
diagnosis, 41
differential diagnosis of, 76
incidence of, 42
noneffectiveness due to, 42
Rural typhus. *See* Scrub typhus.
Russell Islands, 451, 452
RUSSI, S., 250
Russia, 10
Ryukyu Islands, 81, 86

Saar, 343
SABIN, Lt. Col. ALBERT B., 52, 56, 57, 76, 77, 83, 86, 90, 92, 96, 446
Sacral edema, 272
Saddleback fever, in dengue, 72
SADUSK, J. F., Jr., 159, 165
SAENZ, A., 59
SAFFRON, M. H., 279
Saidor, 121
ST. JOHN, J. H., 59
St. Louis encephalitis, 79, 81, 88
Saipan, 288
outbreak of dengue in, 68–70
Salerno, 50, 453, 502
Salicylates, in treatment of rheumatic fever, 232, 233, 235
Salmonellal infection, 491
Samar, 125
Samoa, 496
SAMPSON, J. J., 283n, 299–300, 302
San Francisco Port of Embarkation, 380
Sandflies, 49, 50, 51, 53
Sandfly fever, 7, 16, 49–58, 491
clinical course, 56–57
diagnosis of, 56–57
laboratory confirmation of, 57
differential diagnosis, 57
epidemics of, 50, 56
epidemiology of, 53–55
etiology, 52–53
hospitalization for, 57
immunity to, 55–56
incidence of, 51, 53–55
onset of, 56
reporting of, 50
summary, 57–58
susceptibility to, 56

Sandfly fever—Continued
symptoms, 56–57
treatment of, 57
vector of, 52, 53
virus of, 52–53
Sanding of tent floors, as preventive measure against scrub typhus, 122
Sanitation, factor of, in poliomyelitis, 93, 95
Sansapor, 121, 122, 123, 124, 125
Santa Ana Army Air Base, 233
Sardinia, 53, 453, 502
SARTWELL, Dr. PHILIP E., 5
Saskatchewan, 82
SAYEN, J. J., 128n, 129, 130
SAYERS, Lt. Col. M. H. P., 135
Scabies:
as a venereal disease, 432–433
incidence of, 432–433
Scarlet fever, 1, 226
differential diagnosis of, 76
epidemics of, 226
incidence of, 226, 228
Schick test:
in diphtheria, 278
reactions to:
interpretation of, 297
relation of cutaneous lesions in, 296–297
Schistosomiasis, 198, 491, 528
SCHMIDT, Dr. L. H., 594, 596
SCHNEIDER, Lt. Col. LEO V., 398
SCHOENBACH, Lt. Col. EMANUEL B., 283, 300
School of Tropical Medicine, 499
Schouten Islands, 112
SCHULEMANN, 579
SCHWENKTER, Dr. FRANCIS F., 226
Sclera, effect of Atabrine on, 552
Scott Field, 20, 226
See also Army airfields.
SCOVILLE, A. F., Jr., 210
Scrub typhus, 68, 111–142
antibiotics in, 136
antibodies in, 134
autopsy findings in, 115, 116
chemotherapy in, 136–137
clinical characteristics of, 111
clinical experience with, 112–132
first phase, 112–116
second phase, 116–121
third phase, 121–125
clinical picture of, 112, 113, 118, 128
complications of, 118–119, 131
convalescence in, 123–125, 131
deaths due to, 114, 128
Scrub typhus—Continued
diagnosis:
complement fixation tests in, 134–135
laboratory aids in, 133–136
Proteus OX-K in, 113, 115
strain isolation and identification in, 135–136
Weil-Felix reaction in, 125
differential diagnosis of, 491
disposition of patients with, 123–125
epidemics of, 120, 121
epidemiological study of, 119
eschar of, 111, 113, 115, 117, 122, 123, 125, 126, 128, 130
factor of morale in, 137
fever in, 111, 113, 127
geographic distribution of, 111, 112
immunity to, 137, 138–139
in Chinese troops, 127–128
in India-Burma theater, 127–132
in Japanese troops, 128
in Philippines, 125–126
in South Pacific Area, 126–127
in Southwest Pacific Area, 112–126
incidence of, 112, 113, 121–125
incubation period, 123
investigations of, 116–121
mode of onset, 111
mortality in, 119, 120, 122, 128, 129
orientation in, 112–116
outbreaks of, 120, 121–122
pathology of, 132–133
postwar studies on, 138–139
preventive measures against, 122
prognosis in, 129, 131
rash in, 111, 113, 128
rickettsia of, 111
serotherapy in, 136
severity of, 128, 129
signs of, 111, 113, 126, 130
summary, 139–142
clinical picture, 140
diagnosis, 140–142
natural course, 142
prophylaxis, 142
therapy, 142
symptoms of, 111, 113
treatment, 131, 136–138, 139
vectors of, 111
Weil-Felix reaction in, 119, 127, 133–134
SEAGRAVE, Lt. Col. GORDON S., 499

Season(s):
for measles, 32
for pneumonias, 17, 20
malarial, 500, 502
Seasoning of troops, 23
military importance of, as related to common respiratory diseases, 5, 7
Secretary of War, 144
Section for Research on Minimal Tuberculosis, Medical Research and Development Board, U.S. Army, 379–380, 384
Sedation, as adjuvant therapy:
in meningitis, 270
in tuberculosis, 363
Sedimentation rate, in malaria, 490
Seitz filter, 319, 445
Selective service registrants, examination of, 344
Senior Consultant in Dermatology, European theater, 432
Senior Consultant in Medicine, South Pacific Area, 496
Senior Consultant in Tuberculosis, European theater, 340, 341, 342, 345
Separation centers, tuberculosis detected in troops in, 340
Separation from service. *See* Disability separations.
Serological tests, for—
epidemic typhus, 217
murine typhus, 222
primary atypical pneumonia, 25
Serotherapy, 30
in bacterial pneumonia, 32
in epidemic typhus, 192–194
in meningitis, 264
in scrub typhus, 136
Serum, antimeningococcal, in meningitis, 265
Serum therapy, in lobar pneumonia, 30, 32
Service Command(s):
First, 396
Third, 31, 38, 44
Fourth, 19, 37, 40, 260, 262, 265, 414
Sixth, 29
Seventh, 227, 229
Eighth, 40, 381
Ninth, 227, 283
Servicemen's Readjustment Act of 1944, 390
SETTLE, E. B., 125
Seventh U.S. Army, 155, 453, 504, 506, 507
incidence of sandfly fever in, 51
Sex, factor of, in infectious mononucleosis, 38
Seymour Johnson Field, 46
SHANNON, J. A., 539n, 586
Shillong, 312
Shingbwiyang, 127
Ship fever. *See* Epidemic typhus.
Shock, evidence of, in fulminating meningococcal bacteremia, 253
Shoulder pain, in rabies, 101
Sicilian campaign, 52, 453, 504, 507
Sicily, 8, 50, 51, 52, 53, 165, 451, 453, 502
Siege of Mantua, 449
SIEMSEN, W. J., 324
Sign(s):
Babinski, 88
of dengue, 74
of Japanese B encephalitis, 88
SILER, J. F., 59, 409, 410
SIMMONS, Brig. Gen. JAMES S., 59n, 81, 144, 424
Single phase fever, in dengue, 72
SINTON, J. A., 580
Sinusitis, 7, 15
chronic, 1
Sister Kenny method, in poliomyelitis, 98
Sixth U.S. Army, 121, 466
Skeletal muscles, involvement of, in epidemic typhus, 216
Skin:
abscesses of, complicating typhus, 220
discoloration of, in suppressive malaria therapy, 466, 476
effect of Atabrine on, 552–553, 556
involvement of, in epidemic typhus, 216
Skin lesions, associated with malaria, 517
See also Cutaneous diphtheria.
SMADEL, JOSEPH E., 99, 100, 138, 195, 447
Smallpox, confused with typhus, 217
Smears, from cutaneous lesions, *Corynebacterium diphtheriae* in, 293–294
SMITH, P. K., 223
SMORODINTSEV, investigator of epidemic influenza, 10
SN 6, 911. *See* Sontochin.
SN 7, 618. *See* Chloroquine diphosphate.
SN 8, 137. *See* Oxychloroquine.
SN 13, 276. *See* Pentaquine.
SNYDER, Dr. JOHN C., 136, 180n, 188, 192, 193, 195, 197
Sodium benzoate, 196
Solomon Islands, 126, 279, 359
Solomon Islands campaign, 280, 492
Sontochin, 559–562
absorption, 559
clinical testing of:
for suppression, 560–561
in acute attacks of *vivax* malaria, 560

Sontochin—Continued
general properties of, 559
in *falciparum* malaria, 559, 560, 561
in *vivax* malaria, 559, 560
plasma levels of, 559, 561
toxicity of, 561
Sontoquine, in treatment of malaria, 512
Sore throat:
in infectious mononucleosis, 39
peritonsillar cellulitis as complication of, 4
streptococcal, 8
South America, 82, 366
South Pacific Area, 9, 279, 284, 453, 454, 460, 468, 479, 488, 496, 498
diphtheria in, 279–280
malaria in, 495–498
scrub typhus in, 126–127
Senior Consultant in Medicine in, 496
tuberculosis in, 357–360
diagnosis of, 358–359
evacuation for, 360
incidence of, 357–358
mortality in, 360
types of, 358
Southwest Pacific Area, 95, 112–126, 130, 227, 288, 453, 454, 458, 460, 466, 475, 476, 479, 481, 482, 488
diphtheria in, 282
malaria in, 452, 498
poliomyelitis in, 96
scrub typhus in:
directive on, 124
first cases of, 112–115
incidence of, 121–125
investigations of, 116–121
measures for control of, 121–125
outbreaks of, 120–121
tuberculosis in, 360–362
diagnosis of, 361
evacuation for, 362
incidence of, 360–361
special medical problems in, 361–362
Spanish-American War, 330, 450
Specialized centers:
establishment of, 387
for treatment of tuberculosis, 381–388
Speech disturbances, in Japanese B encephalitis, 88
SPILLMAN, R., 331
Spinal fluid:
in cerebral malaria, 485
pleocytosis in, 38, 57, 89
protein levels of, in diphtheritic neuritis, 300
SPITZ, Dr. SOPHIE H., 132, 133, 169, 171, 322
Spleen, 519
enlargement of, in chronic malaria, 487
involvement of, in epidemic typhus, 216
palpable:
in diagnosis of malaria, 506
in infectious mononucleosis, 39
rupture of, 486, 496
technique of palpating, 482
Splenectomy, 41
Splenic infarction, complicating scrub typhus, 119
Splenic pain, in relapsing *vivax* malaria, 487
Splenomegaly, 508
in Fort Bragg fever, 438
in malaria, 482
Spontaneous pneumothorax, 372–375
admissions and readmissions for, 373
problem of, 374
See also Pneumothorax.
Spring-summer encephalitis, Russian, 79, 82, 84
Sputum:
meningococci in, 259
pneumococci in, 8, 9
Sputum control, in tuberculous patients, 378–379
Staphylococcus, 27
Staphylococcus aureus, 293
STAR (Specialized Training and Reassignment) unit, poliomyelitis in, 97
Station hospitals:
in chain of evacuation, 508
malaria patients in, 485
period of hospitalization for, 508–509
treatment of, 508
role of, in—
diagnosis of tuberculosis, 333
disposition of tuberculous patients, 381
See also Hospitals, station.
Statistical Health Report (WD Form 86ab), 28, 29, 49, 50, 51, 96, 227, 241, 357, 503
Statistics:
dengue, 65
malaria, 449–463, 514–517
attack rates, 454, 456, 457, 458
deaths, 460–461
duration of hospitalization, 459
relapse rates, 455–459
types, 454–455
rheumatic fever, 228–229
STEIN, Capt. S. C., 398
Sternal puncture, in malaria, 489

639243°—63——44

STERNBERG, T. H., 415, 419, 420
Stibophen, 432
Stiff neck, in poliomyelitis, 97
Stilwell Road, 127
STONE, Col. WILLIAM S., 194
STRATMAN-THOMAS, W. K., 484
Streptococcal infection(s), 4
  directives on, 7–8, 227. *See also* Directives.
  epidemicity of, 228
  epidemics of, 227
  in Mediterranean theater, 7
  in Zone of Interior, 6
  incidence of, 228
  penicillin therapy for, 9
  sulfadiazine in treatment of, 9
  sulfonamide prophylaxis for, 227, 228
"Streptococcal sore throat," directive on application of term of, 8
Streptococcus, 10
  hemolytic, 2, 33, 275
    group A, 226, 259
    infections due to, 4, 7
Streptococcus viridans, 17–18, 32
Streptomycin, 382
  effect of, on scrub typhus, 136
STROHL, A., 301
STRONG, R. P., 143
STUART-HARRIS, C. H., 188
Stupor, in rabies, 101
Suaba, 451
Subcommittees, of National Research Council:
  on tropical diseases, 493
  on tuberculosis, 374, 384
  on venereal diseases, 409, 413, 419, 420, 423, 424, 425, 426, 430
Sulfadiazine, 30, 32, 34, 35, 259, 260, 262, 263, 266
  effect of, on—
    cervical lymphadenitis, 6
    falciparum malaria, 529
    parasitemia, 512
  in bacteremia, 271
  in gonorrhea, 412
  in lobar pneumonia, 30
  in meningococcal infections, 246, 247, 249, 262
  in streptococcal infections, 6, 9
  policy for administration of, 242
Sulfamerazine:
  effect of, on *falciparum* malaria, 529
  experimental field test with, 530
  in suppression of malaria, 470
Sulfamerazine—Continued
  inferiority of, to Atabrine, 529
  suppressive activity of, 529
  toxicity of, 529
Sulfamethazine, effect of, on *falciparum* malaria, 529
Sulfanilamide, 196, 262, 263
Sulfapyrazine, experimental field tests with, 530
Sulfapyridine, 262, 263
  in gonorrhea, 411
  in pneumococcal infections, 17
Sulfathiazole, 262, 263
  in gonorrhea, 411, 412
Sulfonamide-resistant gonorrhea, treatment of:
  directives on, 415, 416. *See also* Directives.
  fever therapy in, 412, 413
  penicillin in, 414–418
Sulfonamide therapy, complications of, 262–263
Sulfonamides, 1, 4, 6, 13, 31, 498
  antimalarial activity of, 528–529
  in bacterial pneumonia, 31, 32
  in lobar pneumonia, 30
  in malaria, 470, 512
  in meningococcal infections, 239, 242
  in primary atypical pneumonia, 21
  in rheumatic fever, 227, 228
  in streptococcal infection, 227, 228
  indications for use of, 9
  See also specific drugs by name.
Sumatra, 111
Summary health reports, 28
Supplies, X-ray film, shortage of, 391
Supportive measures:
  in epidemic typhus, 192
  in scrub typhus, 136
Suppressants, 467, 510
Suppression of malaria, 465–477
  blood levels of Atabrine for, 473–476
  effect on parasite species in, 469–470
  effects of Atabrine withdrawal on, 468–469
  factors in early failures in, 466–468
  long-term clinical experience in, 471–472
  penicillin in, 525–526
  quinine in, 531–535
  Sontochin in, 559–562
  sulfonamides in, 470, 528–529
  totaquine in, 536
  undesirable effects of Atabrine in, 476–477
  See also Atabrine; Atabrine suppressive therapy.

Suppressive efficacy, of chloroquine diphosphate, 572–576
Suppressive therapy, for malaria, 452
See also Atabrine; Atabrine suppressive therapy.
Suppuration of glands, complicating dengue, 75
Surgeon General, The, 13, 19, 20, 94, 226, 227, 236, 237, 329, 391, 410, 412, 415, 417, 425, 427, 429, 442, 465, 597
See also Office of the Surgeon General.
Surgical Group, 1st Auxiliary, 341
Surgical treatment:
for bronchiectasis, 45
for orchitis, 37
Survival period:
in fulminating bacteremia, 252, 253
degree of adrenal hemorrhage in relation to, 253, 255
in meningitis, 257, 258
Susceptibility, to—
influenza, 11, 13
measles, 32, 34
sandfly fever, 56
SUTHERLAND, G. F., 300
SUVA, 63
SWANTZ, H. E., 586
Sweats:
in malaria, 482, 487
in Q fever, 106
Swine influenza, 11
SYLVESTER, J. C., 266
"Symposium on Human Malaria," 480
Symptomatology, vague, in malaria, 518
Symptoms, of—
dengue, 72, 74–75
epidemic typhus, 146
Fort Bragg fever, 437
malaria, 481–484
meningococcal bacteremia, 244–245
Q fever, 106–107
rabies, 101–102
sandfly fever, 56
tuberculosis, 354
Syndrome(s):
Guillain-Barré, 300
Waterhouse-Friderichsen, 249, 250, 251, 254–256, 260
Syphilis, 418–430
noneffectiveness due to, 37
serological tests for, effect of malaria on, 490
Syphilis—Continued
treatment of:
intensive arsenotherapy in, 420–423
penicillin in, 423–427
records on, 428–430
See also Directives, pertaining to venereal diseases.
Syphilis register, 420, 425
treatment recorded on, 429
Syria, 318

Tachycardia:
in cutaneous diphtheria, 295
scrub typhus, 124
Tagap, 452, 453
TAKEMORI, N., 195
Tank respirators, 95, 98
Taranto, 106
TATLOCK, Capt. HUGH, 445, 446, 447
TAUSSIG, S., 52
Technical bulletins. *See* Directives, pertaining to specific subject.
Technical memorandums. *See* Directives, pertaining to specific subject.
Technique:
of palpating spleen, 482
of thick-drop blood film, 509
Tellurite medium, 295
Temperate climates, pattern of common upper respiratory infection in, 8
Temperate Zone, 359
Temperature, body, elevated. *See* Fever.
Temperature, factor of, in activating malaria, 480
Temperature curve, in—
Fort Bragg fever, 438
Japanese B encephalitis, 89
malaria, 481, 519
Q fever, 107
scrub typhus, 115
TENBROECK, Dr. CARL, 80
Tendon reflexes, in Japanese B encephalitis, 88
Tension, in relapsing *vivax* malaria, 487
Tent floors, sanding of, as preventive measure, against scrub typhus, 122
Terrain, factor of, in scrub typhus, 121, 122
Terramycin, effectiveness of, in—
bacteremia, 269
meningitis, 269, 273
Q fever, 109
scrub typhus, 139
Tertian malaria, malignant, in India-Burma theater, 498

Test(s):
cold agglutinin, 22, 24, 40
complement fixation, 25
in Brill's disease, 203
in encephalitis, 83, 86, 89
in endemic typhus, 208, 213
in epidemic typhus, 157, 183–188
in lymphocytic choriomeningitis, 100, 101
in malaria, 490
in scrub typhus, 134–135
Eagle, 490
exercise tolerance, in scrub typhus, 123
for cure of gonorrhea, 411
Frei, 431
Hinton, 490
Kahn, 40, 490
Kline, 490
Koh's block, 557
Kolmer, 490
Kuder vocational interest, 390
Mazzini, 490
neutralization:
in encephalitis, 83, 86, 89
in epidemic typhus, 189–190
rickettsial agglutination, in endemic typhus, 213, 215
Schick, in diphtheria, 278, 296–297
serological, 25
in encephalitis, 84, 88
in epidemic typhus, 217
in infectious mononucleosis, 40
in lymphocytic choriomeningitis, 100, 101
in malaria, 490
in murine typhus, 222
in primary atypical pneumonia, 25
Weil-Felix, 104, 119, 125
See also Weil-Felix reaction.
Widal, 40
Tetanus, 100
"The Hump," 113
Theaters of operations, U.S. Army. *See* specific theater.
Therapy:
for meningitis, 262–263
scrub typhus, 119
Thick-drop blood film, in diagnosis of malaria, 509
Thirst, in epidemic typhus, 216
THOMAS, H. M., Jr., 251, 262, 264, 265
THOMAS, L., 86
THOMPSON, K., 581, 587
Throat cultures:
Corynebacterium diphtheriae in, 8
Hemolytic influenzae in, 7
hemolytic streptococci in, 7, 13
pneumonococci in, 7, 8, 13
Thrombophlebitis, complicating scrub typhus, 119, 131
TIERNEY, N. A., 137, 152
TIGERTT, Lt. Col. WILLIAM D., 87
Tinnitus, 484, 534
in epidemic typhus, 216
TOMPKINS, V. N., 261
Tonsillitis, 1, 8
sulfadiazine in treatment of, 9
Tonsils, 2
TOPPING, Dr. NORMAN H., 190, 443
Totaquine, 498
advantage in use of, 536
comparison of:
with quinacrine, 536
with quinine, 536, 538
in *vivax* malaria, 536
study of qualities of:
at Bushnell General Hospital, 536
at Kennedy General Hospital, 536
in New Caledonia, 536
toxicity of, 536
Toxicity, of—
Atabrine, 466, 495, 498, 550–558
oxychloroquine, 577
pamaquine, 585–589
quinine, 501, 534
totaquine, 536
Trachea, tuberculosis of, 369
TRAIL, Air Commodore R. R., 402
Transmission, mode of, of—
acute respiratory diseases, 1
dengue, 59
epidemic typhus, 143
murine typhus, 204
Q fever, 108–109
Transmission experiments:
in common cold, 3
in infectious mononucleosis, 39
"Transport cold." *See* Common cold.
TRASK, Dr. JAMES D., 226
Trauma, factor of, in cutaneous lesions, 307, 310, 312
Treasury Islands, 451
Treatment, of—
chancroid, 431
common upper respiratory infections, 9

Treatment, of—Continued
cutaneous diphtheria, 304–307
dengue, 76
diphtheria, 278, 304–307
epidemic typhus, 192–201
antibiotics in, 194–195
chemotherapy, 195–200
serotherapy in, 192–194
supportive therapy, 192
fulminant meningococcal bacteremia, 263–265
gonorrhea, 410, 411
Japanese B encephalitis, 90
malaria, 493–524
Atabrine in, 510–511, 538–558
cinchona alkaloids in, 531–538
in South Pacific Area, 495–498
iron in, 512
penicillin in, 525–526
Plasmochin in, 511, 579–592
quinine in, 511–512, 531–535
results of, 514–517
Sontoquine in, 512
sulfonamide drugs in, 512, 528–529
to reduce relapse rate, 513–514
meningococcal infections, 261–270, 271
drug of choice in, 263
neurosyphilis, 428
poliomyelitis, 98–99
Q fever, 108
rheumatic fever, 232–235
sandfly fever, 57
scrub typhus, 130, 131, 136–138
postwar studies on, 139
streptococcal infections, 6
syphilis, 420–427
tuberculosis, 363, 378–390
in prisoners of war, 390–396
Tremors, hand, residual of scrub typhus, 124
Trenchfoot, 103
factor of, in activating malaria, 480
Tribromolthanol, 102
Trigeminal nerve, 258
Trimus of the jaw, complicating dengue, 75
Trinidad, 86, 102
Trombiculae, 126
Trombiculid mite, vector of scrub typhus, 111
Troops:
military importance of seasoning of, as related to common respiratory diseases, 5, 7
Troops—Continued
Negro:
infectious mononucleosis in, 40
mumps in, 38
tuberculosis in, severity of, 354
Trophozoites, of *Plasmodium falciparum*, 529
Tropical diseases, factor, in activating tuberculosis, 360
Tropical typhus. *See* Scrub typhus.
Tropical ulcer, and diphtheria, 279–319
See also Cutaneous diphtheria.
Tropics:
diphtheria in:
among natives, 310–312
among soldiers, 312
incidence of allergic disorders in, 9
Truax Army Air Field, 20
Tsutsugamushi disease. *See* Scrub typhus.
Tubercle bacilli, 344, 354
isolation of, 363
Tubercular diseases, in Civil War, 330
Tuberculosis, 1, 329–407, 491
admission rates, 330, 335, 336, 353–354
aspects of, 367–377
extrapulmonary tuberculosis, 367–370
pleurisy with effusion, 356, 370–372
spontaneous pneumothorax, 372–375
control of, 405–407
death due to, 243, 354, 360, 375–377
diagnosis of, 358–359, 361, 362, 364
differential diagnosis, 354
discharge rates for, 334–339
discovery of—
before induction, 331–333
in service, 333–334
epidemiology of, 356–357
evacuation for, 360, 362, 363, 364, 378–381
historical perspective, 329–331
hospitalization for, 354–355, 359, 378–390
in Army Air Forces personnel, 343–344
in British military forces, 399–403
Royal Air Force, 402–403
Royal Navy, 400–402
in Canadian military forces, 403–405
in captured prisoners of war, 390–396
in Chinese troops, 364
in concentration camps, 349–353
in nurses, 342–343
in oversea areas, 339–367
in recovered Allied military personnel, 346–349
in recovered American prisoners of war, 344–346

Tuberculosis—Continued
in recovered prisoners of war, 390–392
in U.S. Army, 329–339
in Zone of Interior, 340, 378–390
incidence, 334–339, 340, 343–353, 357, 360–361, 362, 364
in Alaskan Department, 365
in China-Burma-India theater, 364–365
in European theater, 339–341
in Far East, 366–367
in Latin American Area, 366
in Mediterranean theater, 353–357
in Middle East, 366
in Middle Pacific, 364
in South Pacific Area, 357–360
in Southwest Pacific Area, 360–362
in Western Pacific Base Command, 362–363
miliary, 350, 358, 367
mortality from, 329, 375–377
nonpulmonary, 367–368
nonpulmonary tuberculous complications of, 383
occurrence of, in oversea areas, 339–367
patients with:
disposition of, 341–342, 355–356
evacuation of, 360, 362, 363, 364, 378–381
orientation of, 388–390
rehabilitation of, 388–390
problems of, 359–360, 361–362, 363
pulmonary, 329, 358
racial resistance to, 375
severity of, in Negro soldiers, 354
significance of Army experience, for control of, 405–407
treatment of, 355–356, 359, 361, 363, 364, 378–399
directive on, 342. *See also* Directives.
specialty centers for, 381–388
under military government in Germany, 397–399
types of, 358
Tuberculosis centers, hospitals designated as:
in Mediterranean theater, 354
in Zone of Interior, 381–388
Tuberculosis Control Division, U.S. Public Health Service, 405, 406
Tuberculous meningitis, 100, 367
Tuberculous patients. *See* Patients.
Tulagi-Florida Islands, 451
Tunis, 49, 453, 502
Tunisia, 24, 49, 53, 354, 453, 495, 502
TURNER, T. B., 415
Type(s):
of pneumococcus, 30
of tuberculosis, 358
Typhoid fever, 491
confused with typhus, 217
Typhus exanthematiqué (French). *See* Epidemic typhus.
Typhus fever, 112
epidemics of, 143
severe, resemblance of cerebral malaria to, 485
See also Epidemic typhus; Murine typhus; Scrub typhus.
Typhus vaccines, potency test for, 190

Ulcer(s):
disability discharge due to, 339
tropical, 279–319
Undifferentiated respiratory disease, 5, 12, 39
virus of, 3, 4, 5
See also Common cold.
United Nations Relief and Rehabilitation Administration, 398
United States. *See* Zone of Interior.
United States Armed Forces Institute, 390
United States of America Typhus Commission, 116, 122, 134, 137, 151, 154, 157, 179
creation of, 144
field laboratories of, 135, 136
study facilities of, 145
University:
Harvard, 39
Indiana, 97
of California, 80, 82
of Chicago, 596, 597
of Colorado, 380, 384, 385
of Maryland, 596
of Notre Dame, 596
of Pennsylvania, 433
Yale, 443, 444
Upper respiratory infection. *See* Common upper respiratory infection.
Urban typhus. *See* Murine typhus.
Urethritis, nonspecific, 418
Urinary frequency, in relapsing *vivax* malaria, 487
Urinary retention, in epidemic typhus, 146
Urogenital tract:
involvement of, in dengue, 76
tuberculosis of, 367
Urticaria, in malaria, 484, 517
U.S. Army Medical Museum, 40

U.S. Army Medical Research and Development Board, Section for Research on Minimal Tuberculosis of, 379–380, 384
U.S. Army Signal Corps, 22
U.S. Army Veterinary Corps, 368
U.S. Marine Corps, 1st Marine Division, 451
U.S. Navy, 13, 144, 228
U.S. Penitentiary, Atlanta, 597
U.S. Public Health Service, 64, 144, 443, 444, 594
  National Institute(s) of Health of, 108, 135
  Tuberculosis Control Division of, 405, 406
U.S.S.R., 81, 82, 86, 143, 349

Vaccination:
  for epidemic typhus, 201
  for influenza, 11, 13
Vaccine(s):
  Cox, 156, 157
  Craigie, 168, 183
  epidemic typhus, 156–172
  influenza, 11, 13
  mouse-brain formalin, 90
VAN RAVENSWAAY, A. C., 20, 45
VAN ROOYEN, C. E., 188
Vasculitis, generalized, acute, in scrub typhus, 125
Vector(s), of—
  dengue, 59, 61
  epidemic typhus, 201
  murine typhus, 205
  sandfly fever, 52, 53
  scrub typhus, 111
V–E Day, 433, 435
Vella Lavella, 451
Venereal diseases:
  control program for, 434–435
  diagnosis of, 409–435
  directives on. *See* Directives, pertaining to venereal diseases.
  historical note, 409–410
  induction of registrants with, 433–434
  minor types of, 430–433
  treatment of, 409–435
  See also specific diseases.
Venezuela, 102
Venezuelean encephalitis, 79, 82, 86
Ventilation, factor of, on incidence of respiratory diseases, 7
Vertigo, in treatment with totaquine, 536
Veterans' Administration, 332, 339, 375, 383, 385, 386, 387, 388, 389, 390, 392
  transfer of tuberculous patients to, 388
Veterans' hospitals, admission to, for tuberculosis, 332
Veterinary Corps, 368
VIEUSSEUX, M., 239
Vincent's angina, 8, 9
Vincent's infections:
  admission rates for, 5
  complicating infectious mononucleosis, 41
  penicillin therapy for, 9
  sulfadiazine in treatment of, 9
Vincent's organisms:
  appearance of throat lesions produced by, 4
  in common upper respiratory infection, 2
Virus(es), of—
  common cold, 3
  encephalitis, 82
  mumps, 35, 36
  influenza, 2
    A, 10, 12, 13, 14
    B, 11, 12, 13, 14
  undifferentiated respiratory disease, 3, 4, 5
Virus and Rickettsial Diseases Laboratory, 133
Virus encephalitides, arthropodborne, 79–91
Vision, blurring of:
  in cerebral malaria, 485
  in treatment—
    with dihydroquinine, 537
    with totaquine, 536
Visual acuity, effect of Atabrine on, 501
Visual disturbances, factor of chloroquine diphosphate in, 575
Vivax infections:
  chloroquine diphosphate in, 560–561
  relapse rate in, therapeutic regimen for reduction of, 513–514
Vivax malaria:
  acute attacks of, 540–542
    quinacrine hydrochloride in, 540–542 543
    quinine in, 532
    Sontochin in, 559–562
  chloroquine diphosphate in, 562, 563–571 572–576
  deaths due to, 461
  due to blood infections, 526
  factor of antimony compounds in precipitating clinical attacks of, 528
  naturally acquired, 528
  oxychloroquine in, 577
  Plasmochin naphthoate in, 579–592
  prodromal symptoms of, 481
  relapses of, 487, 496, 532

Vivax malaria—Continued
splenomegaly in, 482
sulfonamides in, 529
See also Malaria.
Vocational interest test, Kuder, for tuberculous patients, 390
Vocational Rehabilitation Act, 390
VOELCKER, A. F., 252
V-J Day, 70, 334
Volturno River, 502
Volunteers:
for experiments in—
dengue, 76
malaria, 470
sandfly fever, 52, 56, 57
for study of murine typhus vaccine, 210
in clinical trials of antimalarial drugs, 574, 575, 577, 596, 597
in trials of Atabrine, 494
Vomiting, in—
dengue, 72
malaria, 483
meningococcemia, 245, 253, 262
pancreatitis, 36
poliomyelitis, 97
sandfly fever, 56
suppressive malaria therapy, 466, 494, 534, 556
treatment with totaquine, 536
Von Economo's disease, 80

Waikiki Beach, 63
Wakde Task Force, 121
WALSHE, F. M. R., 299
Walter Reed Army Medical Center, 447
War Between the States. *See* Civil War, American.
War Department Circular No. 109, 26 Apr. 1943, 383
War Department General Orders No. 6, 13 Feb. 1923, 429
War Department Prisoner of War Circular No. 11, 8 Feb. 1944, 393
War Department technical bulletins, pertaining to—
diphtheria, 283
meningococcal infections, 266
neurotropic virus diseases, 79, 86, 88, 100, 101
rheumatic fever, 227, 232, 236
tuberculosis, 370, 388, 389
venereal diseases, 415, 416, 425, 427, 428, 429, 430
See also Directives.
War fever. *See* Epidemic typhus.
War Production Board, 531
WARING, Dr. JAMES J., 47, 374, 380, 384
WARNER, Maj. FRANK B., 104
WARREN, R. O. Y., 52
WARSHAUER, S. E., 124
Wasting, in chronic malaria, 487
Water transportation, care of tuberculous patients during, 378
Waterhouse-Friderichsen syndrome, 249, 254–256, 260
in fulminant meningococcal bacteremia, 251, 252
WAUD, Maj. SIDNEY P., 499
WD MD Form 86ab, 28, 357
See also Report(s).
WD MED Form 78, Syphilis Register, 420, 425, 429
See also Syphilis register.
Weakness,
in attacks of malaria, 481, 487
in meningococcal bacteremia, 245, 253
in Q fever, 106
muscular, in murine typhus, 221
WEBSTER, Col. BRUCE P., 124
WEBSTER, Dr. L. T., 81
WEED, Dr. LEWIS H., 493
Wehrmacht, 51, 52, 395
WEICHSELBAUM, A., 239
Weight loss, in Q fever, 107
WEIGL, 156
Weil-Felix reaction, 40
in epidemic typhus, 157, 179–183
in Fort Bragg fever, 441
in Q fever, 103, 104
in scrub typhus, 119, 125, 127, 133–134
in typhus, 157, 181, 182
See also Reaction(s).
Weimar, 353
WEINBERG, L. D., 255
Wellcome Research Laboratories, New York, 597
WERTMAN, K., 181, 182, 183, 210
WEST, J. B., 586
West Africa, 529, 532
Western equine encephalomyelitis, 79, 80, 82, 88
Western Pacific Base Command:
tuberculosis in, 362–363
diagnosis of, 362–363
evacuation for, 363
incidence of, 362
special problems, 363
treatment of, 363

WHITTAKER, S. R. F., 56
WILLIAMS, Lt. Col. S. W., 113
WOLBACK, 152
WOOD, Col. FRANCIS C., 128, 499
WOODWARD, Maj. THEODORE E., 125, 151, 152, 154, 194, 208, 210
World War I, 5, 34, 36, 41, 80, 225, 243, 275, 330, 334, 368, 375, 450
  death rate from lobar pneumonia during, 29
  deaths from disease in, 1
  measles in the Army during, 32, 33
  meningococcal infections during, 239
  mumps in, 35
  tuberculosis in Army during, 332
Wright's stain, in diagnosis of malaria, 509
WYMAN, Capt. STANLEY M., 104

Xenopsylla cheopis, 205
X-ray examination. *See* Roentgenographic examination.
X-ray facilities, for diagnosis of tuberculosis, 361

Yale University School of Medicine, 443, 444
Yellow fever, 65, 82
YEOMANS, A., 151, 152, 193, 194, 197
Yugoslavia, 180, 192

ZARAFONETIS, C. J. D., 134, 136, 157, 180, 184, 186, 197, 211, 212
ZIMMERMAN, Lt. Comdr. H. M., 90
ZINSSER, H., 143, 202
Zone of Interior, 340, 479, 516, 517
  antimalarial drug studies in general hospitals in, 536
  bacterial pneumonia in, 28–31
  common upper respiratory infection in, 5–6
  evacuation of paralytic patients to, 98
  infectious mononucleosis in, 40–41
  influenza in, 12–14
  measles in, 34–35
  mumps in, 37–38
  primary atypical pneumonia in, 19–21
  Q fever in, 103, 106
  study of cutaneous diphtheria in hospitals of, 282–283
  tuberculosis in:
    admission rates, 336
    hospitalization for, 378–390
    in captured prisoners of war, 393–396
    incidence rates for, 340
    specialty centers for treatment of, 378–388
    treatment of, 378–390

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