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REPORT NO. P-1898

DATE April 24, 1942

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SUBJECT

Prophylaxis and Treatment of Burns Caused by
Chemical Warfare Agents

(1) Treatment of Mustard Burns with S-461
Ointment in a Series of Controlled
Experiments on Human Subjects

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NAVAL RESEARCH LABORATORY

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NAVY DEPARTMENT

Report on

Prophylaxis and Treatment of Burns Caused by
Chemical Warfare Agents

- (1) Treatment of Mustard Burns with S-461
Ointment in a Series of Controlled
Experiments on Human Subjects

NAVAL RESEARCH LABORATORY
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Washington, D. C.

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of Ships," dated 16 December 1940

Date of Tests: April 1942

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AUTHORIZATION

1. This work was authorized under Project 547/41 - "Maintenance, Bureau of Ships," dated 16 December 1940. The problems which were proposed for a study were given in Bureau of Ships letter S-S77-2 (D2), Serial #811 of 17 December 1940, Sections 3 and 7.

2. In modern warfare where chemicals may be used as weapons either in defensive or offensive action there are casualties of several types. The casualties due to burns may be minimized by action either before, i.e. prophylaxis, or after, i.e. treatment; exposure to the chemicals. In this report the results of a study of the treatment of one of the chemical warfare agents - mustard (β -dichloro diethyl sulfide) after it had been applied to the skin is given. In the next report will be given the results of experiments where the mustard is applied to skin protected by S-461 ointment, i.e. prophylaxis.

3. In the protection against or neutralization of mustard, among the agents used in the first World War were dichloramine T, chloramine T or azochloramide. These chemicals can be compounded into an ointment and applied to the skin. As the stability of these compounds is not satisfactory a study has been in progress in the Chemical Division of this Laboratory to obtain compounds that have greater stability toward hydrolysis, heat and so forth and one of these compounds obtained, S-461, has been used as the active ingredient in the ointment used in this study.

4. The ointment developed is of the vanishing cream type and consists of the active agent, S-461, in triacetin with magnesium stearate as the thickening agent. The spreading qualities of this ointment has been shown to be excellent and it has the added advantage of feeling and acting like a "non-greasy" type. The formulation of this ointment base is the result of work carried out by the National Defense Research Committee at the University of Wisconsin under the direction of Dr. Homer Adkins working in collaboration with members of the faculty of the School of Pharmacy. The active ingredient, S-461, was developed and is controlled by this Laboratory.

5. The triacetin was chosen as the anhydrous medium for this formulant base because it is inert toward the active ingredient and has been shown not to have an injurious effect on the skin. It is commercially available in excellent quality. Magnesium stearate was chosen as the thickening agent because it gives the ointment the properties of a vanishing cream. The active ingredient S-461 was chosen due to its stability in the ointment base and its rapid reaction with mustard gas. The resulting ointment is stable and will resist chemical or physical decomposition indefinitely at temperatures as high as 120° F. and will not break at 50° F.

6. At this stage the ointment was thought to be ready for clinical investigation. The experiment was conducted as follows:

7. Sixty-three volunteers were obtained from among active Naval personnel. They were assigned numbers and were catalogued as to complexion and whether or not they sunburned easily. The skin on the ventral surfaces of the forearm was used for the experiment. The left arm was used as a control and the right arm for the test. The vesicant agent was re-distilled Levenstein mustard of about 98% purity. The method of application was a standard 2 cc. tuberculin syringe with a No. 26 gauge, 1/2" length hypodermic needle. The size of the drop from this needle was determined beforehand and was found to vary between 5 - 15 milligrams in weight and had an approximate diameter of 2 - 3 millimeters. The subject placed both forearms in a horizontal position and four drops of mustard was applied, two on each forearm, the drops being approximately 8 cm. apart. Immediately after application the two distal drops were wiped off thoroughly with dry cotton gauze and the protective ointment rubbed in the right forearm over the affected area, being first applied about 3 cm. from the center of the affected spot and rubbed in a circular motion and an inward spiral until the center was reached and covered. The subject then moved to one side and at the end of three minutes after the application of the mustard, the time being checked by a stopwatch, the two proximal drops of mustard were removed by wiping thoroughly with dry cotton gauze and the ointment applied to the right proximal area as previously outlined. The application part of the experiment was then complete and the subject's skin was now in the following condition:

8. On the right forearm there were two applications of ointment on two areas which had been respectively exposed to mustard for a period of approximately 15 seconds and three minutes, and on the left forearm there were two areas that had been respectively exposed to mustard for a period of approximately 15 seconds and three minutes and then had been wiped dry and no further protection applied. All subjects were told not to remove the ointment manually and to endeavor to keep their hands away from the affected areas. No dressings were applied. The subjects were next seen 24 hours later and the first series of readings were taken at this time and also 22 photographs were taken. The majority of these photographs show typical reactions and the balance of them are the few atypical reactions. All other reactions not photographed were normal reactions. The method of reading the reactions was as follows:

9. It was first stated whether the lesion was basically a macule, papule, or vesicle, next, erythema was noted as very light, light, moderate, or severe. Also the diameter of the lesion was measured in cm., this measurement applying to the diameter of the total lesion. Any unusual reactions were also noted; i.e., annular vesicles and numerous small vesicles and a few cases of self-innoculation from the original lesion were noted. At the 24-hour stage a few of the subjects had large vesicles on the three-minute control lesion and it was thought advisable to drain them and apply a protective dressing. At the end of 72 hours, counting from the original application, the lesions were again read on the same basis. At this time all lesions were subsiding and there seemed to be no advantage in recording the lesions any further because, in our opinion, the maximum effect of both the vesicant agent and the ointment had been reached. None of the lesions became secondarily infected. The experimental data and pictures are appended. Table I summarizes the results as observed at the end of 24 hours, Table II, the results at the end of 72 hours. The numbers on the pictures apply to the numbers on the tables. Those pictures with a "0" preceding the number apply to the second series, which is not to be confused with the second reading. All pictures were taken at the time of the first reading.

10. At the end of 24 hours, in the 15-second test, out of 63 cases there were three vesications despite the application of the ointment. Out of the 63 control tests there were 56 vesications. In the 63 3-minute tests there

were 31 vesications. In the 63 three-minute control there were 61 vesications.

11. The 72-hour readings may be summarized as follows:

In the 15-second test in 63 cases there were four vesications and three of the lesions had disappeared completely. In the 63 15-second control there were 52 vesications. In the 63 three-minute tests there were 32 vesications. In the 63 three-minute control there were 56 vesications, five having subsided since the previous reading.

12. No differences were noted in the skin reactions of blondes and brunettes. In Test #2, for example, 22 cases of vesication were obtained from 45 brunettes treated; nine cases of vesication were obtained from the 18 subjects with fair complexion (16 blondes and 2 redheads). Thus, approximately 50% gave vesication in each complexion group.

13. In our opinion, if the ointment containing S-461 compound is applied immediately to an area of human skin from which mustard liquid or vapor has been removed immediately, the chances of vesication following are very slight. If there is a moderate delay, i.e., 3 - 5 minutes, vesication will follow in about half the cases but the degree of vesication will be greatly reduced.

CODE

1. M = Macule
2. P = Papule
3. V = Vesicle
4. E = Erythema

ll = Very light

l = Light

m = Moderate

s = Severe

5. A = Annular Vesicle

All # = Diameter of lesion in cm.

S = Lesions subsiding

S.R. = Subsiding rapidly

TABLE I

TEST FOR HS CONTROL

24-Hour Readings

No.	Com- plexion	Sun- burn	Control #1	Test #1	Control #2	Test #2	Remarks
0	Brunette	No	VEM 1 1/2	PEM 1	VEM 4 1/2	PEM 3	
1	Brunette	No	VEL 1 1/2	PEL 1/2	VEL 3	PEM 1 1/2	
2	Brunette	Yes	VEM 1	PEL 1	VEM 3	VEM 3	
3	Brunette	No	VEL 1	PEL 1/2	VEL 1 1/2	PEL 2 1/2	
4	Blonde	Yes	VEM 1 1/2	PEL 1	VES 2 1/2	PEM 3	
5	Blonde	Yes	VEL 2	PEL 1/2	VEM 4	PEM 3 1/2	
6	Blonde	Yes	VEM 2 1/2	MEL 1	VES 4	VEM 3	slight ves.#2T
7	Brunette	No	VEM 1	MEL 1/2	VEM 4	VEM 2 1/2	" " "
8	Brunette	Yes	VEM 1	MEL 1	VEM 3	PEM 2 1/2	
9	Brunette	Yes	VEM 2 1/2	MEL 1 1/2	VEM 3 1/2	VEL 2	
10	Brunette	Yes	VEM 1	MEL 1	VEM 2	PEM 4	
11	Brunette	No	VEM 1 1/2	PEL 1 1/2	VEM 3	PEM 3 1/2	
12	Brunette	No	VEM 1	MEL 1	VES 4	PEM 3 1/2	
13	Brunette	No	VEM 1 1/2	MEL 1 1/2	VEL 3	VEM 3	
14	Brunette	Yes	VEM 2	PEL 1 1/2	VEM 3 1/2	VEM 3	
15	Brunette	Yes	VEL 1	MEL 1/4	VES 4	PEM 3	
16	Brunette	Yes	VEL 3/4	PEL 3/4	VEM 2 1/2	PEL 1	
17	Brunette	No	VEM 1 1/2	PEM 1 1/2	VEM 3	PEM 3	
18	Brunette	No	VEL 1 1/2	MEL 1	VEM 3	VEM 2 1/2	
19	Brunette	No	VEM 1	MEL 3/4	VEM 3A	VEM 1 1/2	
20	Brunette	No	VEM 1 1/2	MEL 1	VEM 3	VEM 4	Test #2 completely dry before appli- cation of S-461
21	Blonde	No	VEM 1	MEL 1/2	VEM 3 1/2A	VEM 2	
22	Brunette	No	VEM 1	MEL 1/2	VEM 3	MEM 2 1/2	
23	Brunette	Yes	PEM 1 1/2	MEL 1	VEM 3	PEM 3	
24	Blonde	Yes	VEM 1 1/2A	MEL 1	VEM 4 1/2A	VEM 3 1/2	Test #2-dry before S-461.
25	Brunette	No	VEM 1	PEL 1 1/2	VEM 4A	VEM 2 1/2	
26	Blonde	No	VEM 2	MEL 1/2	VEM 4A	VEM 2	
27	Blonde	Yes	VEM 1 1/2	PEM 1	VEM 4 1/2	VEL 2	
28	Brunette	Yes	VEM 1 1/2	PEL 3/4	VEM 3A	VEM 1 1/2	
29	Brunette	No	VEM 1 1/2	MEL 1/2	VEM 3A	VEM 1 1/2	
30	Blonde	Yes	PEM 1 1/2	0	VEM 3	MEM 3	
31	Brunette	Yes	MEM 1	MEM 1	VEM 2 1/2	PEM 3	
001	Blonde	Yes	VEM 1 1/4	PEL 1/2	PEM 3 1/2A	PEM 3	
002	Brunette	Yes	VEM 1 1/4	MEL 3/4	VEM 2 1/2	PEM 4	

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TABLE I (Continued)

No.	Com- plexion	Sun- burn	Control #1	Test #1	Control #2	Test #2	Remarks
003	Brunette	No	VEM 3/4	MEL 1/4	VEM 2	PEM 2 1/2	
004	Brunette	No	PEM 3/4	PEL 3/4	VEM 2 1/2	PEM 3 1/2	
005	Brunette	No	VEM 1 1/2	VEM 1 1/2	VEM 3 1/2A	VEM 2 1/2	
006	Brunette	Yes	VEM 1 1/2	PEM 2	VEM 2 1/2	PEM 3	
007	Brunette	Yes	PEM 1	MEL 1	VEM 4 1/2A	VEM 2 1/2	
008	Brunette	No	VEM 1	PEL 1/2	VEM 3A	PEM 2 1/2	inoculated acci- dently by subject
009	Blonde	No	VEM 3/4	PEM 3/4	VEM 3/4	VEM 1/4	(see picture)
010	Blonde	Yes	VEM 1	MEL 1/2	VEM 1A	MEM 2	
011	Brunette	No	VEM 1	PEM 1	VEM 2	PEM 3 1/2	
012	Blonde	No	VEM 1	PEM 1	VEM 3 1/2A	VEM 1	
013	Brunette	No	VEM 1	PEM 1	VEM 2 1/2	VEM 1	
014	Brunette	No	PEM 1/4	VEM 3/4	VEM 4 1/2A	VEM 3	Many small vesi- cles on Test #2
015	Brunette	Yes	VEM 1 1/4	MEL 1	VEM 2 1/2	PEM 2	Several small ves. on Test #2.
016	Brunette	No	VEM 1	MEL 1/2	VEM 4 1/2A	PEM 4	
017	Brunette	No	VEM 1 1/2A	PEM 1	VEM 4A	VEM 2	
018	Brunette	No	VEM 2 1/2A	PEM 1	VEM 4 1/2A	VEM 1 1/2	
019	Brunette	No	VEM 1	PEM 1	VEM 4A	VEM 1	
020	Blonde	Yes	VEM 1	PEM 1	VEM 5 1/2A	VEM 2	
021	Blonde	No	VEM 1A	PEM 1/2	VEM 3 1/2A	VEM 2	Many small vesi- cles Test #2
022	Brunette	No	VEM 3/4	PEM 1/2	VEM 2 1/2	PEM 3	Many small vesi- cles Test #2
023	Blonde	Yes	VEM 2	MEL 1	VEM 2 1/2	PEM 1 1/2	
024	Brunette	No	VEM 1	PEL 1	VEM 3 1/2A	VEM 1 1/2	
025	Brunette	Yes	VEM 1/2	PEL 1	VEM 4	VEM 2	Many small vesi- cles Test #2
026	Blonde	No	PEM 1 1/2	PEM 1/2	PEM 3 1/2	PEM 4	
027	Brunette	No	VEM 1	PEM 1	VEM 4 1/2A	VEM 3	Many small vesi- cles Test #2. Self inoculated (See picture)
028	Redhead	Yes	VEM 1	PEM 1/2	VEM 2	PEM 2 1/2	
029	Brunette	No	VEM 1	PEM 1	VEM 3	PEM 3/4	Many small vesi- cles control #1
030	Brunette	No	VEM 1A	PEM 1	VEM 3 1/2A	PEM 3	1 small vesicle Test #2
031	Redhead	Yes	VEM 1A	PEM 1	VEM 3 1/2A	PEM 4	Many small vesi- cles Text #2

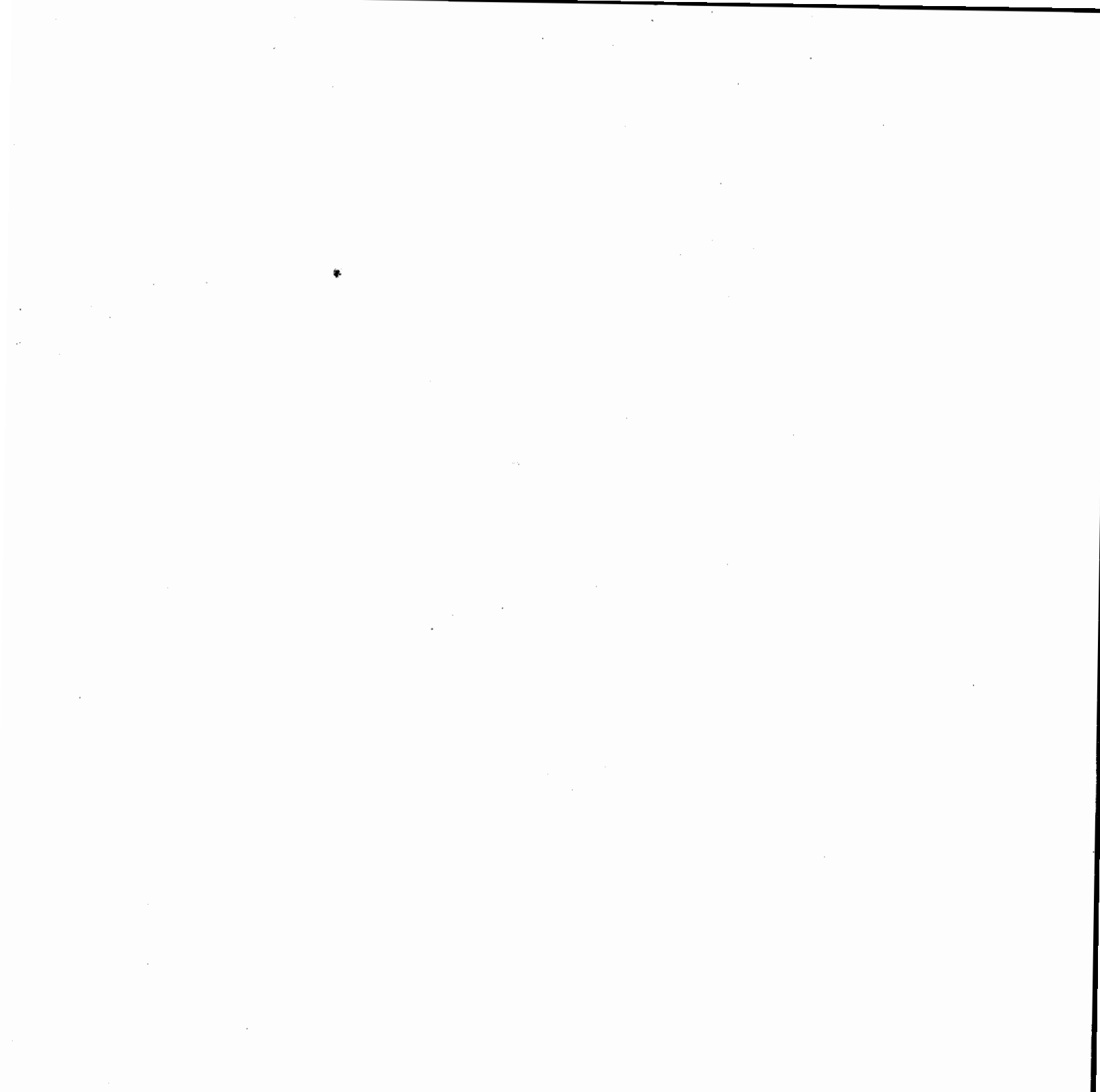


TABLE II

TEST FOR HS CONTROL

72-Hour Readings

No.	Control #1	Test #1	Control #2	Test #2	Remarks
0	VEM 1 1/2	PEM 1	VEM 4 1/2	PEM 3	
1	VEL 1 1/2	PEL 1/2	VEL 3	PEM 1 1/2	S.
2	VEL 1 1/2	MEL 1/2	VEM 3 1/2	VEM 2 1/2	Sub. R.
3	VEL 1	MELL 1/2	VEL 2	PEL 2	S.R.
4	VEM 2	MEL 1	PEM 3 1/2	MEM 3	S.R.
5	VEL 1	PELL 1/2	VEM 4	VEL 2 1/2	S.R.
6	VEM 3	PELL 1	VEM 4	VEM 2	Sub.
7	VEM 1	MEL 1/2	VEM 3	VEL 2	S.
8	VEL 3/4	MELL 1/2	VEM 3	PEL 2	S.R.
9	VEM 2A	MEL 2	VEM 3 1/2A	VEM 3	S.
10	PEM 1 1/2	MEL 1	PEM 2 1/2	PEM 3 1/2	S.R.
11	VEM 1 1/2	MELL 1	VEM 2 1/2	VEM 2	S.R.
12	PEM 1 1/2	MEL 1/2	VEM 4	PEM 3	S.R.
13	Pock 3/4	MEM 1	VEM 3A	VEM 3	S.R.
14	VEM 2	PEM 1	VEM 3	PEM 3	S.R.
15	VEM 1/2	MELL 1/2	VEM 3 1/2	MEM 2 1/2	S.R.
16	VEM 1/2	PEL 3/4	PEM 2	PEL 1/2	S.R.
17	VEM 1 1/2	PEM 1	VEM 2 1/2A	VEM 2 1/2	S.R.
18	PEM 1	MEL 1	VEM 4A	VEM 2 1/2	S.R.
19	PEM 1	MEL 1/2	PEM 2 1/2	PEM 1 1/2	S.R.
20	PEM 1 1/2	PEL 1	PEM 3	PEM 4 1/2	S.R.
21	VEM 1	MELL 1/2	VEM 3A	VEM 2	S.R.
22	PEM 1 1/2	PEL 1/2	VEM 2 1/2	PEM	S.R.
				Many V	
23	PEM 1/2	VEM 1/4	VEM 2 1/2	MEM 2 1/2	S.R.
24	VEM 1 1/2	PEM 1	VEM 4A	PEM 3 1/2	S.R.
25	VEM 1	PEL 1	PEM 3 1/2	VEM 2 1/2	S.R.
26	VEM 2	MELL 1/4	VEM 4A	PEM 2	S.R.
27	VEM 1	PELL 1/2	VEM 4A	VEM 3 1/2	S.R.
28	VEM 1 1/2	PEL 1/2	VEM 2	VEM 1 3/4	S.R.
29	VEM 1 Pock	MELL 1/2	VEM 3A	VEM 3	S.R.
30	VEM 1/2	0	VEM 2 1/2	MELL 2	S.R.
31	PEM 3/4	PELL 3/4	VEM 2 1/2	VEM 2 1/2	S. Many small vesicles
001	VEM 1 1/2	MELL 1/2	VEM 3A	PEM 2	S.R.
002	PEM 1 Pock	MELL 1/2	VEM 2	PEM 2 1/2	S.R.
003	VEM 1	PEL 1/2	VEM 2	VEM 2	S.R. Many small vesicles #4
004	VEM 3/4	MEL 1/2	VEM 2 1/2	PEL 2 1/2	S.R.

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TABLE II (Continued)

No.	Control #1	Test #1	Control #2	Test #2	Remarks
005	VEM 1 1/2	VEM 11 Pock	VEM 3	VEM 2 1/2	S.R.
006	VEM 1 1/2	PEM 2 1/2	VEM 2 1/2	PEM 2 1/2	S.R.
007	VEM 1/2	MELL 1/2	VEM 4 1/2A	PEM 3 1/2 Pock	S.R.
008	VEM 1 1/2	PELL 3/4	VEL 3/4	PEM 1/2	S.R.
009	PEL 1/2 Pock	PELL 1/2	VEM 3	VEM 1	S.R.
010	VEM 1	PEL 1/2	VEM 1 1/4	PEL 1 1/4	S.R.
011	VEM 1 1/4	PEL 1	VEM 2	PEL 3	S.R.
012	VEL 1	PEL 1/2	VEM 3	VEL 2	S.R.
013	VEL 1 1/2	PEL 3/4	VEL 2 1/2	PEM 2 1/2	S.R.
014	VEL 1 1/2	VELL 1 1/4	VEL 4	VEL 2	S.R.
015	VEL 1	0	VEL 2 1/2 M.S.V.	VEL 1 1/4 M.S.V.	S.R.
016	VEL 1	PELL 1/2	VEL 4A	VEL 2 M.S.V.	S.R.
017	VEL 1/4	PEL 1	VEL 4A	PEL 2 1/2	S.R.
018	VEL 2	VEL 1/2	VEM 4 1/2	VEL 2	S.R.
019	Pock 1-M	MEL 1/2	VEM 3 1/2	Pock 3/4 L	S.R.
020	VEL 1	PEL 1/2	VEL 5A	VEM 2	S.R.
021	VEL 1	PELL 3/4	VEM 3A	VEL 1/2	S.R.
022	VEM 1	MEL 1/2	VEM 2 1/2	VEM 2 1/2	S.R.
023	VEM 2	MELL 1/2	VEL 2 1/2	VEL 1	S.R.
024	Pock 1/2 M	PEL 1/2	VEM 3A	VEM 2	S.R.
025	Pock 1/2 M	MEL 1/2	VEM 3	MEL 2	Skin removed - healing well
026	VEL 3/4	0	PEL 3	PEM 3	S.R.
027	VEM 1	PEL 1	VEL 3 1/2	PEL 3	S.R.
028	VEM 1	PEL 3/4	Pock 1 1/2L	VEM 1 1/2	S.R.
029	VEL 1	PEL 1	VEM 3	PEM 3/4	S.R.
030	Pock M-1	PELL 1	VEL 3A	VELL 1	S.R.
031	PEL 1	PEL 1	VEL 3	VEL 2	S.R.



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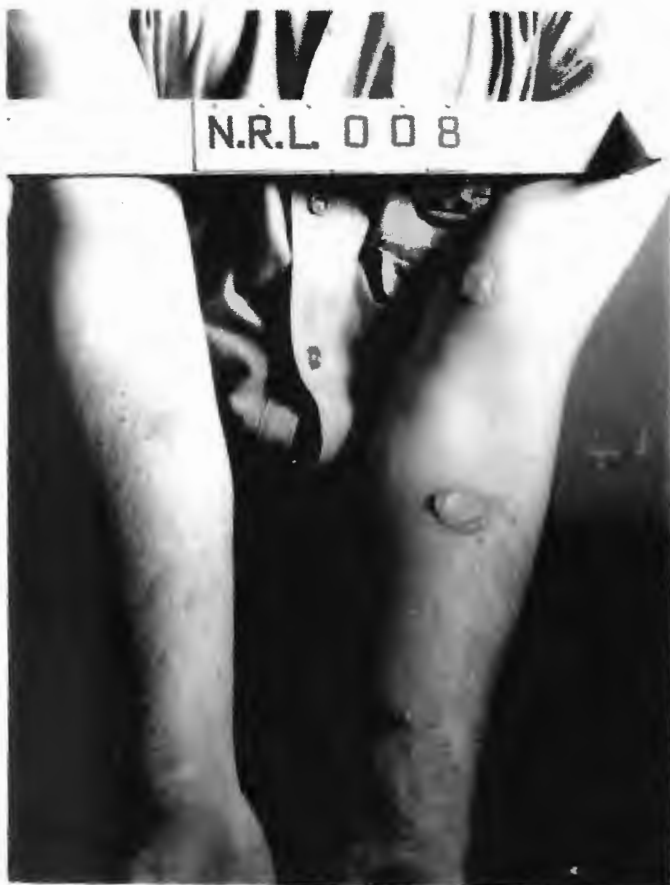




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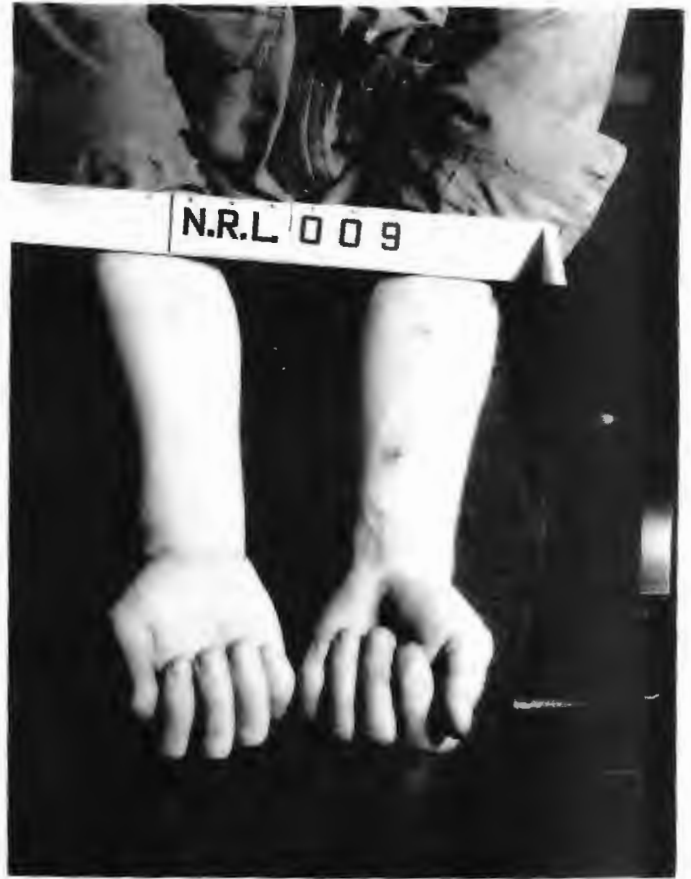


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