

AVIATION MEDICINE SPECIAL (CAN) REPORTS
VENEREAL DISEASES MINUTES

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NATIONAL RESEARCH COUNCIL
Division of Medical Sciences
acting for
COMMITTEE ON MEDICAL RESEARCH
of the
Office of Scientific Research and Development
Subcommittee on Venereal Diseases of the
Committee on Chemotherapeutics and Other Agents

NOT FOR PUBLICATION
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NATIONAL RESEARCH COUNCILMinutes of a Conference of the Panel on Penicillin in Syphilis

Washington, D.C. 3 December 1943.

On the 3rd of December, 1943, there was held in Washington a Conference of the Panel on Penicillin in the treatment of syphilis in human beings. Present were the following:

Dr. J. E. Moore, Chairman, Dr. John F. Mahoney, Lieut. Col. T. B. Turner, Comdr. W. H. Schwartz, and by invitation, Dr. Harry Egle. Dr. Barry Wood was unable to be present.

The Chairman reported that Dr. Evan Thomas had treated 10 patients with early syphilis with a total dose of 60,000 units of penicillin and ten with 200,000 units. Dr. Thomas has been much concerned over the delay in obtaining negative darkfield examinations which, in the 60,000 unit group, required about 96 hours, and in the 200,000 unit group about 48 hours. Dr. Thomas believes these dosages of penicillin to be probably inadequate and to raise the possibility of immediate infectious relapse in a large proportion of patients so treated. He has expressed himself as wishing to be relieved of the responsibility of treating patients with such small doses because of the public health hazard involved, and the impossibility of maintaining patients in the hospital for a long enough period of time to guard against relapse.

On the other hand, Dr. Harold Cole from Cleveland reports that he has treated ten patients with the total 60,000 unit dose with much more rapid disappearance of spirochetes from lesions than is reported by Dr. Thomas. In nine such patients darkfield examinations became negative from 7½ to 18 hours after the start of treatment. Dr. Cole also reports satisfactory healing of lesions of patients in this group.

Dr. Arthur Schoch, utilizing a total dose of 600,000 units, reports 16 patients treated, all but 2 of whom were darkfield negative, ^{within 18 hrs.} the other 2 in 36 and 41 hours respectively. The healing of lesions on this dosage schedule is, he reports, strikingly rapid.

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Dr. Mahoney reports 19 cases treated with 1,200,000 units, the Navy 16 cases and the Army 3 cases at this same dosage schedule, the results in each conforming to Dr. Lahoney's original 4 patients.

With regard to intravenous as contrasted to intramuscular injections, Dr. Cole reports 5 patients treated by continuous intravenous drip for 2 days, 200,000 units per day, with atypical spirochetes persisting in 3 of these patients for from 3 to 5 days.

Dr. Barnett likewise reports that one patient treated intravenously some weeks ago with a total dosage of a million units in 5 days, has just relapsed 7 weeks after treatment.

Relative to the probable curative efficacy of dosage schedules, Dr. Eagle reports that in experimental animals a total dose of 400 - 1,000 units per kilogram of body weight is necessary to render a chancre darkfield negative, and to bring about healing. On the basis of the node transfers so far done (all at 6 weeks after treatment), the curative dose is probably a ten-fold multiple of the healing dose. The largest total dose at which a positive node transfer has been observed at 6 weeks is 8,000 units per kilogram (administered twice daily for 4 days). If these animal results are directly translatable to human beings, the minimum expected total curative dose in early syphilis is 600,000 plus units.

Dr. Eagle reports that a number of different treatment schedules have been or are being tried in his laboratory, as follows:-

A single dose of penicillin in whatever size and whether administered intravenously, intramuscularly, or subcutaneously, is uniformly unsuccessful.

Three groups of animals are being treated with a total duration of 4 hours, the interval between treatments being divided into 3 groups: (a) intravenous drip for 4 hours; (b) one injection every 15 minutes; and (c) one injection every hour.

Three groups of animals are being treated with a total duration of 16 hours' treatment: (a) by intravenous drip; (b) injections one every hour; and (c) injections one every 4 hours.

Three groups of animals are being treated with total duration of 4 days' treatment: (a) by intravenous drip; (b) injections every 4 hours for 5 doses daily; and (c) daily injections.

So far there have been no striking differences in disappearance time of spirochetes or healing of lesions between any of these schedules except the ineffectual single dose schedule.

Dr. Mahoney was unable to report the details of animal experiments being carried out in his laboratory; although several hundred animals are under treatment.

Dr. Eagle next reported on his studies of penicillin plus napharsen.

The results are as follows:-

- 1) Penicillin and napharsen are pharmaceutically compatible.
- 2) When penicillin, 2,000 units per kilogran is administered intramuscularly simultaneously with varying dose of napharsen intravenously, there is no demonstrable effect on the toxicity of napharsen.
- 3) If napharsen and penicillin are mixed in vitro in a concentration of 20 mg. of napharsen per cc. and 12,000 units of penicillin per cc., and the mixture allowed to stand one-half hour before intravenous injection, there is no effect on the toxicity of napharsen.

The conclusion from these experiments is that penicillin has no deleterious effect on the toxicity of napharsen as judged by the death of rabbits.

4) As to therapeutic activity: if napharsen, in a concentration of 10 mg. per cc. and penicillin in a concentration of 128 units per cc. are mixed in vitro, the spirocheticidal activity of the penicillin is not reduced. This does not exclude the possibility of a loosely bound reversible chemical combination between penicillin and napharsen. Nevertheless, a concentration of napharsen 2 to 20 times as great as in the projected therapeutic schedules for human beings, does not adversely affect the spirocheticidal activity of penicillin.

5) The effect of relatively large amounts of penicillin on the trypanocidal activity of small amounts of napharsen was studied. The mixture of the two drugs was less trypanocidal than napharsen alone; and the longer the mixture was allowed to stand before in vitro testing, the more the trypanocidal activity of napharsen was cut down. However, with concentrations of napharsen comparable to those attained in the body with therapeutic doses (1 to 50,000 to 1 - 1,000,000), 500 to 1,000 units of penicillin were required for a significant diminution of napharsen effect. The less napharsen present, the less penicillin was required to inhibit its action. The inhibiting in vitro dose of penicillin was 50 - 100 times as great as in any concentrations which might be obtained in the human body with the proposed treatment schedule.

Under these circumstances there is no contraindication to the immediate clinical trial of combined penicillin-napharsen schedules. This trial seems desirable to the panel because of the possibility that in many patients some treponemes may be penicillin resistant but destroyed by napharsen, and vice versa.

These data led to a general discussion of the proposed treatment schedules outlined in the Minutes of the October 29, 1943, Conference on Penicillin in the treatment of syphilis. The panel agreed that Group I of these original schedules i.e., 1,000 units of penicillin every 3 hours to a total of 60,000 units, would probably be ineffectual; and for this reason and also because of the public health reasons advanced by Dr. Thomas, this physician at Bellevue Hospital was released from the responsibility of trying any further patients on this schedule. However, in order to demonstrate the inefficacy of this treatment schedule and further to resolve the discrepancies between the results of Doctors Cole and Thomas, it was agreed that Dr. Cole be asked to continue on this same schedule until he has completed a total of 40 patients; and that Dr. Moore be asked to undertake the treatment of

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10 patients by this same schedule. These with the 10 patients already treated by Dr. Thomas, will provide a total of 60 patients in this group.

The treatment groups and the clinics to utilize them were then completely reorganized according to the following schedule.

<u>Group</u>	<u>Unit dose</u>	<u>No. doses</u>	<u>Total dose penicillin</u>	<u>Total dose napharsen</u>	<u>Clinics and approximate No. pts. to be treated</u>
1	1,000	60	60,000	---	Thomas 10 (finished) Cole 40 Moore 10
1-a	1,000	60	60,000	320 mg.	Cole 60
2	5,000	60	300,000	---	Schoch 100 Barnett 75
2-a	5,000	60	300,000	320 mg.	Becker 150
3	10,000	60	600,000	---	Thomas 250 - 300 Becker 60
3-a	10,000	60	600,000	320 mg.	Army 150
4	20,000	60	1,200,000	---	Navy) Army) Mahoney) 300 Cox)

At this point Dr. Mahoney reported that he would not require his allocation of 18,000,000 units per month from OSRD since he was now being supplied from U.S. Public Health Service sources.

The rearrangement of schedules outlined above requires some reallocation of monthly supplies of penicillin which from this date on should be as follows:-

<u>Investigator</u>	<u>Units of penicillin per month</u>
Cole	3,000,000
Schoch	10,000,000
Barnett	8,000,000
Becker	27,000,000
Thomas	30,000,000
Cox	16,000,000

These allocations utilize 94,000,000 of the 100,000,000 units allotted by the Committee on Chemotherapeutics. It was agreed that the additional 6,000,000 were to be at the disposal of the Chairman of the penicillin panel to provide for unexpected

demands from present clinics.

The Chairman of the panel was directed to call to the attention of all participants in the study the following points:-

- 1) The penicillin allotted is for the treatment of syphilis only, and is not to be used for panic cases of other infections.
- 2) No publication of penicillin results is to be undertaken by any individual clinic without OSRD approval.
- 3) All penicillin failures are to be dropped from this study and are not to be retreated with penicillin. They may be retreated by any other system desired by the clinic in question.

The Chairman was directed to enquire of Doctors Schoch and Barnett as to whether the number of cases under treatment each month by them can be increased, each of these investigators using treatment schedule No. 2.

Dr. Mahoney reported that the proposed blank for reporting cases had been prepared and mailed to members of the panel, but that return comments had not yet been received. The Chairman agreed as soon as the blanks were prepared in final form to have them printed and distributed to all participating clinics. The Chairman was directed to enquire of Dr. J. R. Keller, U.S. Public Health Service, as to whether the franking privilege could be utilized for the return of such reports.

The panel further agreed that the Chairman might ask Doctors S. Barry Wood and Francis Blake to undertake the treatment of such patients as are available to them by one of the treatment systems outlined above. Each of them will be asked to use treatment system 2-2.

The panel also agreed that as soon as penicillin supplies become available, the drug be furnished for a further study of late syphilis to Doctors Paul G'Leary, Walsh McDermott, and Harry Solomon. A minimum of 20,000,000 units per month will be required for each of these clinics.

The panel further agreed that for the time being it was undesirable to bring into the study any further clinics for the treatment of early syphilis.

The meeting then adjourned.

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Medicine
Chemotherapeutics (Venereal Diseases) #2629

NATIONAL RESEARCH COUNCIL
Division of Biological Sciences

COMMITTEE ON MEDICAL RESEARCH
of the

Office of Scientific Research and Development
Committee on Medicine
SUBCOMMITTEE ON VENEREAL DISEASES

Minutes of the twenty-first meeting
11 November, 1943

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The twenty-first meeting of the Subcommittee on Venereal Diseases, National Research Council, was held at the National Academy of Sciences in Washington on 11th of November, 1943. Present were the following:

- From the Subcommittee on Venereal Diseases, Doctors J. E. Gore, J. H. Stokes, Oscar F. Cox, John F. Mahoney, and N. A. Nelson. Dr. Russell Herrold was absent.
- From the United States Army, Majors Thomas H. Sternberg and Robert Dyar.
- From the United States Navy, Comdr. W. H. Schwartz.
- From the U. S. Public Health Service, Doctors Otis L. Anderson and Harry Eagle.
- From the Food and Drug Administration, Doctors Herbert O. Calvery, Geoffrey Woodard, and Edwin P. Lang.
- From the Office of Civilian Defense, Dr. Benjamin Miller
- From NRC Doctors Lewis H. Wood, O. H. Perry Popper, J. L. Caughey, Jr., Joseph Wearn, George Guest, and Philip S. Owen.
- From NRC-CAR, Dr. T. R. Forbes
- From CAR, Dr. E. C. Andrus.

The Minutes of the last meeting were approved. ✓

The Chairman stated that this meeting had been primarily called at the request of Dr. John F. Mahoney for the purpose of obtaining suggestions as to priority and trial of prophylactic substances in the human experiment concerning inoculated gonorrhoea at the Federal Prison at Terre Haute, Indiana. ✓

At the request of the Chairman Dr. Mahoney submitted the following report:

It is desired to present the following brief report of progress in the study of prophylaxis in gonorrhoea being carried out through the use of human volunteers in the federal penitentiary at Terre Haute, Indiana. Following approval of the project and the making of funds available by the Office of Scientific Research and Development, a lapse of several months was required for preliminary arrangements. The actual opening of the study took place on September 21st, 1943, when medical and technical personnel arrived at the institution.

Physical Arrangements

The prison authorities carried out such structural alterations as were

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required to convert suitable space into a laboratory, office, examining room, and general utility room. Complete laboratory equipment was made available from the stocks of the Venereal Disease Research Laboratory; those items to be returned or replaced through purchases made from the account of the study. This expedient avoided the delay which would have been experienced if essential items of equipment had been secured through purchase prior to the opening of the study.

Personnel

Two medical officers and two bacteriologists were assigned to the study. All were given preliminary training in the laboratory and clinical phases of gonorrhoea. The staff appears to be adequate in size, although subsequent additions to the technical group may be found necessary.

Selection of Volunteers

It was considered advisable to approach the prison population, in a search for volunteers, through the medium of small groups rather than mass appeal. More than 100 prisoners have signed the necessary forms and have received the approval of the prison authorities for participation in the study. The manner and the extent of the response has been surprising. The volunteers are subjected to detailed medical examination before being included in the study. At the present writing a total of 27 volunteers have been utilized.

Technique of Exposure

The method of exposure consists of the introduction into the distal portion of the urethra of varying amounts and varying concentrations of culture strains of the gonococcus. The material is instilled by use of a tuberculin syringe with a specially devised tip prepared from a rubber catheter. The volunteer remains quiet for a period of from one to one and three-quarter hours. The canal is then cleared by urination and the volunteer permitted to resume his usual activity.

Strains of Gonococcus

It was desired to gain basic information as to the feasibility of conveying actual disease to human volunteers through the medium of culture strains of the gonococcus. In this preliminary phase of the experiment four (4) strains have been employed. Two of these strains were four (4) and five (5) years of age, respectively. They were found to be avirulent even when relatively large amounts of infecting material were employed. Two additional strains were isolated from patients who were placed at the disposal of the study by the Terre Haute Department of Health. Utilizing those strains, when approximately three (3) weeks of age, and employing a relatively large infecting dose, a group of six volunteers were exposed in the usual manner; 0.2 cc. of a McFarland No. 10 suspension was instilled 1-1/2 inches into the urethra and permitted to remain for 1-3/4 hours.

Results

Five of six volunteers exposed in the above manner developed typical

gonorrhoea before the 49th hour; the remaining patient was classified as having gonorrhoea after 84 hours. However, the amount of material used and the infecting routine gave rise to irritative symptoms which appeared shortly after the exposure or merged with the classical symptoms of gonorrhoea.

Discussion

The next essential step in the work is the determination of an infecting dose and a routine which will produce disease without giving rise to postinoculative irritative symptoms. This is mandatory in order that too great a burden will not be thrown upon the agents which are to be evaluated as to their prophylactic efficiency. If irritation from inoculation is not eliminated, the conditions which would exist at the time of application of the prophylactic agent would make it impossible to differentiate between the irritation due to exposure and that produced by the agent. If irritative symptoms are necessary to the production of an infection, a corollary study as to the irritative qualities of each prophylactic agent will be necessary.

Of the freshly isolated strains, the disease produced by Terre Haute No. 1 was found to yield to sulfathiazole therapy. The infection produced by Terre Haute No. 2 failed to respond to sulfathiazole but was readily managed by use of penicillin.

The first group of volunteers inoculated with organisms of the acceptable virulent strain, Terre Haute No. 1, is now under observation. In this group the infecting dose has been reduced to 0.05 cc. of a McFarland No. 10 suspension, diluted 250 times. This group has not shown evidence either of irritation or of disease, although the observation period is not complete.

Solution of the problem of maintaining a virulent strain which will infect without producing local irritative phenomenon probably constitutes one of the most important steps in the study and will largely determine the advisability of continuing the work. Rapid loss in virulence due to age and culture passages would render experimental studies hazardous and would require, as a corrective measure, the frequent passage of a strain through a volunteer.

It will become difficult to carry the work through to a successful conclusion unless volunteers are almost universally infectible with a non-irritating inoculum and unless the strain may be maintained at full virulence without frequent recourse to human passage.

Cooperation

It is a pleasure to mention that the degree and character of the cooperation being extended by the prison authorities leaves nothing to be desired.

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In further discussion of this report, Dr. Mahoney pointed out that the two freshly isolated strains obtained in Terre Haute had been tested for sulfonamide resistance in vitro. However, with Terre Haute strain No. 1 three infected patients were all promptly cured with sulfathiazole. With Terre Haute strain No. 2 all three infected patients were sulfathiazole resistant, and were subsequently cured with penicillin.

The Chairman then submitted a report dated 10 November, 1943, from Dr. Justina Hill, summarizing the results of her studies to date on prophylactic tests in mice with gonorrhoea. Dr. Hill's report follows:

1. Method

This has been described elsewhere but may be briefly described here. Immature female mice, "shocked" by the intraperitoneal injection of blood albumin, are inoculated per vaginam with 0.05 ml. of an infusion broth suspension of 6 hour chocolate agar cultures. The number of organisms, as determined by plate counts, is generally 1,000,000 to 5,000,000 per inoculum. This is adequate to give satisfactory controls, and it has been found that when higher numbers of gonococci are used, drugs which are effective against the smaller number lose their prophylactic action. As soon as Dr. Mahoney can determine minimal infective doses in man, it will be possible to establish more accurately the correct experimental inoculum, which should include an allowance of additional organisms for protection in exceptional cases.

Treatment is given per os or per vaginam usually 2 hours after inoculation, mice are kept at a temperature of about 20° C. and vaginal cultures are taken 24 hours after inoculation. This is done by washing out the vagina with 0.05 ml. of infusion broth after curettage. This material is streaked on 2 chocolate agar plates, which are examined after 48 hours' incubation for the presence and number of gonococcal colonies.

2. Findings

The results are shown in the accompanying table. Tests have been made with concentrations of drug suitable for clinical use, except for the stronger Zephiren concentrations. When the upper limits of action of Argyrol and of silver picrate are determined, it will be possible to make comparisons of parallel dilutions.

In the concentrations studied Argyrol, silver picrate, No. 3 (Eagle) 1:200 and No. 85 (Eagle) 1:200 have been the most effective and have been significantly superior in action to sulfamerizine or sulfathiazole per os, to both of these drugs and to sulfadiazine per vaginam. These experiments will be continued until the limits of action are determined and until 50 per cent end points can be calculated.

The technique is available to test any drugs which seem worthy of study for prophylactic use, and any suggestions will be welcome.

Drug	Dilution	Time of application	Total No. of mice	No. slowing gonococci	Number of colonies
Argyrol	1:10	2 hrs.	20	0	
	1:20	" "	10	0	
Silver picrate**	1:400	" "	18	3	2, 30, about 50 colonies
Zephiran	1:50	" "	18	2	8 and 22 cols.
	1:200	" "	4	1	2 cols.
	1:1000	" "	10	2	40 and 100#
	1:2000	" "	4	3	30, 100#, 100#
No. 115 (Eagle)	1:200	" "	7	4	
	1:1000	" "	3	2	
No. 1001 (Eagle)	1:200	" "	9	5	
	1:1000	" "	8	4	
No. 144 (Eagle)	1:200	30 min.	4	2	15 and 100% cols.
	1:200	1 hr.	4	1	1 col.
	1:200	2 hrs.	9	2	8 and 5 cols.
No. 3 (Eagle)	1:200	2 hrs.	6	0	
	1:500	" "	11	5	4 to 150 cols.
	1:1000	" "	18	9	2 to 200 ccis.
	1:2500	" "	11	5	2 to 150 cols.
	1:5000	" "	19	13	Heavy
	1:10,000	" "	5	4	
No. 85 (Eagle)	1:200	" "	5	1	2 cols.
	1:500	" "	8	3	3, 50 and 100 cols.
	1:1000	" "	18	9	2 to 150 cols.
	1:2500	" "	12	7	3 to 200 cols.
	1:5000	" "	7	6	4, 7, 25 and 100% x 3
Sulfathiazole <u>per os</u>	4 gas/60 kg.	2 "	15	12	Heavy
Sulfathiazole <u>per vaginam</u>	crystals	2 "	12	7	Heavy
Sulfamorizine <u>per os</u>	4 gas/60 kg.	2 " <u>pre-inoc.</u> 30 min.	4	3	Heavy
	"	<u>post-inoc.</u> 1 hr.	4	4	all 200% cols. all 100 to 200% cols
	"	<u>post-inoc.</u> 2 hrs.	4	3	all 150 to 200%
	"	<u>post-inoc.</u>	4	3	8, 10 and 50 cols.
Sulfadiazine <u>per vaginam</u>	1% sodium salt.	2 hrs.	5	4	6, 8, 19, and 100 cols.

* In all of these experiments, the controls, treated with water only were 90 to 100% positive, the growth in general being 150 or more colonies.

** This preparation in jelly was provided by John Wyeth & Bros. The jelly base without the silver picrate is inactive by this test.

* * *

In discussion of Dr. Hill's report the discrepancy was pointed out between the results obtained by her with the oral administration of sulfonamides and those obtained in human beings in field trials in the U. S. Army and Navy. A telephonic enquiry to Dr. Hill elicited the information that her strains had^{not} been tested for sulfonamide resistance. She is to be requested to carry out such tests and to amplify her oral sulfonamide results with the utilization of a sulfonamide-sensitive strain, if possible.

These data supplied by Doctors Mahoney and Hill led to a general discussion of the desirability of use of sulfonamides as local prophylactic agents. Conflicting evidence was presented as to whether in clinical practice results in the treatment of gonorrhea with sulfonamides are less satisfactory now than a year or more ago. Army experience indicates that this is not true and that the results in hospitalized patients are approximately as good as previously. The suggestion was made that the apparently lowered cure rate in civilian clinics might be due to the fact that such clinics saw only, or in large proportion, sulfonamide failures, where as a high proportion of patients might still be undergoing cure as a result of self-treatment of treatment by general practitioners.

It was pointed out that the Army has undertaken in 7 stations a field trial of a calomel-sulfathiazole ointment and that if local sulfathiazole is ineffectual in the prophylaxis of gonorrhea, the Army will wish to abandon this field trial as promptly as the information can be obtained.

It was therefore moved and seconded that, assuming eventual success in the determination of a minimal infecting dose of gonococci, Dr. Mahoney be requested to test first the prophylactic activity of the particular calomel-sulfathiazole ointment now under field trial by the U. S. Army. If this ointment is successful in the prevention of gonorrhea, Dr. Mahoney is next asked to study the effect of its component parts, e.g., calomel alone, and sulfathiazole alone. The next substances to be studied for prophylactic effect are to be the silver proteinate.

Dr. Mahoney states that the several prophylactic substances to be studied will be tested at two and six hours after exposure.

The subcommittee next considered the Minutes of a Conference on Penicillin in the treatment of syphilis in human beings, held 29 October, 1943. These Minutes have previously been circularized. The subcommittee approved the Minutes as read.

The chairman amplified certain points which had been left unsettled in those Minutes. He reported that after conference with Dr. Koefler it seemed desirable to include the Cleveland group in a study of early syphilis. The work with penicillin in Cleveland is under the general direction of a committee composed of Doctors Wearn, Gyorgy, and Cole. Dr. Wearn, who was present at the meeting, reported that this group was entirely willing to enter into a cooperative study of the effect of penicillin in the treatment of early syphilis in the manner indicated in the Minutes of the Conference on Penicillin; that approximately 25 patients per month could be treated; and that 25 hospital beds were available at Lakeside, City, and Children's Hospitals.

The Subcommittee thereupon moved that the Cleveland group through Dr. Cole be invited to participate in such a study and that this group be asked to undertake the treatment of approximately 75 patients with early syphilis, equally divided between Groups I and IV, as listed on pages 2 and 3 of the Minutes of the Conference on Penicillin. These are, respectively:-

Group I- 60 doses of penicillin to a total of 60,000 units

Group IV- as in Group I, plus 320 mg. of napharsen

It was pointed out that in the allocation of treatment groups to clinics as listed on page 5 of the Minutes of the Conference on Penicillin, all groups except I and IV had already been covered by the inclusion of two or more clinics; and that the above request to the Cleveland clinic will provide a study of Groups I and IV by each of two clinics (Thomas at Bellevue, Cole in Cleveland).

The requirements of the Cleveland group for the treatment of 75 patients with 60,000 units of penicillin each will be 1,500,000 units of penicillin per month.

The chairman next pointed out that Dr. Keifer and the Committee on Chemotherapeutics desired to continue the participation of Doctors Barry Wood in St. Louis and Francis Blake in New Haven in this study, but that the Committee on Chemotherapeutics would furnish penicillin to Drs. Wood and Blake for this purpose over and above the allocation of 100 million units per month to the Subcommittee on Venereal Diseases. The chairman of the subcommittee was directed to ask both Drs. Wood and Blake to participate in the planned investigation in the same manner as the clinics selected by the Conference on Penicillin and detailed in its minutes, i.e., by reports sent currently to the chairman Subcommittee on Venereal Diseases on all cases treated.

The chairman next pointed out the action of the Conference on Penicillin concerning the desirability of participation, as soon as supplies of penicillin are adequate, of Doctors Loren Shaffer, Detroit, and Dr. A. Benson Cannon, New York, for early syphilis; and Dr. Paul O'Leary, Rochester, Minn., Walsh McDermott, New York, and Harry Solomon and H. Houston Merritt, Boston, for late syphilis. The subcommittee approved this action of the Penicillin Conference and it is now to be transmitted to the Committee on Chemotherapeutics for its approval.

The chairman stated that Dr. Keifer, in anticipation of the approval of his committee, had already undertaken to supply penicillin in the amount specified to the persons named in the Minutes of the Conference on Penicillin. Excepted only from this arrangement is the Chicago group (Dr. S. William Becker) for which a supply of penicillin has been held up pending the obtaining of the necessary information concerning a combination of napharsen and penicillin.

As to this latter point the chairman pointed out that the Penicillin Conference had agreed that the combined penicillin-napharsen groups would not be started on treatment until it had been demonstrated that (a) napharsen and penicillin are pharmaceutically compatible; (b) each does not increase the toxicity of the other for experimental animals; and (c) each does not materially reduce the in vitro effect of the other. In respect of these points Dr. Eagle reported as follows:-

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- 1) Mapharsen and penicillin are pharmaceutically compatible.
- (2) Penicillin, administered intramuscularly in a dose of 2,000 units per kilogram, immediately following the intravenous administration of 15 mg/kg of mapharsen (this is slightly greater than the L.D. 50 of mapharsen) has no effect on the toxicity of mapharsen in rabbits.
- (3) Penicillin in a dose of 8,000 units per kilogram mixed with mapharsen and allowed to stand in vitro for 30 minutes, slightly decreased the toxicity of the mapharsen when the mixture was administered intravenously. However, this is within the possible limits of experimental error since only 6 animals were studied.
- (4) Studies on the toxicity of penicillin have not been attempted and are not contemplated, partly because of the inadequacy of penicillin supply and partly because of its demonstrated known toxicity.
- (5) A solution of mapharsen 1:100 has no effect on the in vitro spirocheticidal action of penicillin, the latter in a dose of 32 units per cc.
- (6) Penicillin in a dose of 2,000 units per cc. had no effect on the in vitro trypanocidal action of a 1:20,000 solution of mapharsen.

These preliminary results indicate (a) that mapharsen and penicillin are pharmaceutically compatible; (b) that neither increases the toxicity of the other for experimental animals; and (c) that neither materially reduces the in vitro effect of the other. However, before the penicillin-mapharsen treatment systems are inaugurated in human beings, Dr. Eagle feels that these experiments should be repeated and verified; and promises the results within a minimum period of two to four weeks. The subcommittee agreed on the basis of this information to postpone treatment of Groups IV and V, as outlined in the Minutes of the Conference on Penicillin.

Dr. Mahoney reported that the record form is practically completed and will be circularized to members of the Penicillin Panel within the next few days.

With respect to the duplicate serologic testing of specimens from penicillin-treated patients, as outlined in paragraph 4, page 6, of the Minutes of the Penicillin Conference, it was felt by the subcommittee that there were certain technical and administrative details which would make it difficult, if not impossible, for duplicate specimens from all patients to be sent at regular intervals to Dr. Mahoney's laboratory. There was also a general discussion of the desirability of duplicate serologic testing of this type and differences of opinion were elicited.

As a result of this discussion it was agreed by the subcommittee that each clinic would be asked to perform serologic tests at stated intervals, utilizing a quantitative test by whatever technique in current use in that clinic; that the clinic of Evan Thomas would send duplicate specimens to Dr. Mahoney's laboratory but that other participating clinics would not for the time being be asked to do so.

If, at a later date, the information gained in Dr. Mahoney's laboratory from a study of patients in Dr. Mahoney's own clinic and that of Dr. Thomas seems to indicate the desirability of such elaborate serologic investigation, the subcommittee will be reapproached.

Dr. Stokes next reported on a series of conferences which had been held in Philadelphia on the evaluation of false positive blood serologic tests after multiple blood donations. The first of these meetings was on October 22nd. As a result of them it has been agreed by the Subcommittee on Venereal Diseases, the American Red Cross, Dr. Stokes, and various other persons in the University of Pennsylvania, to set up an organized study of this problem in Philadelphia. Capt. Bernard has been transferred for this purpose from the Columbus American Red Cross Blood Donor Center to the University of Pennsylvania under Lieut. Col. A. P. Hitchen. The collaboration has been agreed upon of various persons including Dr. Stokes and members of his staff at the Institute for the Control of Syphilis; Dr. Fred Boerner Major Charles Rein of the Army Medical School, Dr. Herbert Lund of Cleveland, and Drs. Beard and Neurath of Duke University, (the latter two being OSRD contract holders for a study of various phases of the biologic false positive problem).

This report has eventuated in a proposal for OSRD contract from Dr. John H. Stokes, Dr. Fred Boerner, and Lt. Col. A. P. Hitchens, University of Pennsylvania.

This proposal for contract in the sum of \$17,825. was next considered by the Subcommittee on Venereal Diseases, Dr. Stokes having left the room. It was accepted and rated A

The Subcommittee next considered a proposal for OSRD contract from Dr. John H. Stokes, University of Pennsylvania for a study of the effect of penicillin on certain aspects of syphilis. This contract is in the amount of \$22,550. Dr. Stokes having left the room the Subcommittee voted to accept this proposal and to rate it A.

The Subcommittee then considered a proposal for contract from Dr. Even W. Thomas, New York University College of Medicine, for a study of the treatment of early syphilis with penicillin. This contract is for a minimum amount of \$720. and a maximum amount of \$1080. The proposal was accepted and rated A.

The chairman then reported the results of a conference with Dr. Katharine Anderson, Vanderbilt University, concerning her work on the cultivation of the probable etiologic agent in granuloma inguinale and its relationship to the prophylaxis of this disease.

The meeting then adjourned.

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Dr. Forbes

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NATIONAL RESEARCH COUNCIL
Division of Medical Sciences
acting for
COMMITTEE ON MEDICAL RESEARCH
of the

Office of Scientific Research and Development
Subcommittee on Venereal Diseases of the
Committee on Chemotherapeutics and Other Agents
Minutes of a Conference on Penicillin in the Treatment
of Syphilis in Human Beings

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Held in Washington, D.C. 29 October 1943.

On the 29th of October, 1943, there was held in Washington a Conference of a panel approved by the Committee on Chemotherapeutics and Other Agents and by the Subcommittee on Venereal Diseases to arrange for a study of penicillin in the treatment of syphilis in human beings. Present were the following:-

Members of the panel - Drs. J. E. Moore and J. F. Mahoney from the Subcommittee on Venereal Diseases, and Dr. Barry Wood, Jr. from the Committee on Chemotherapeutics and Other Agents.

From the Subcommittee on Venereal Diseases Drs. John H. Stokes and Oscar F. Cox.

Clinic Directors invited by the Subcommittee on Venereal Diseases (including Drs. Mahoney, Stokes, and Cox from the above) Drs. Evan W. Thomas, Bellevue Hospital, New York, C. W. Barnett, Leland Stanford, Jr. University, San Francisco, Arthur Schoch, Dallas Syphilis and Venereal Disease Clinic, Walsh McDermott, New York Hospital.

From the Committee on Medical Research - Drs. A. N. Richards, E. C. Andrus, G. M. Guest, A. Baird Hastings, and J. R. Caughey.

From the Committee on Medicine- Dr. O. H. Perry Pepper.

From the National Research Council- Drs. T. R. Forbes, W. M. Clark, J. M. Sprague, and G. H. Carden, Jr.

From the U.S. Army- Brigadier General Hugh Morgan, Lieut. Col. R.A. Prentiss, Jr., Lieut. Col. T. B. Turner, Majors J. P. Scholtz, Robert Dyar, Charles Rein, and T. H. Sternberg.

From the U.S. Navy- Capt. W. W. Hall, Comdr. W. H. Schwartz and Comdr. F.R. Bailey, Lieut. Comdr. Ralph D. Turner, Lieuts. E. C. Barksdale, G. J. Thompson, and A. M. Hutter.

From the U.S. Public Health Service - Drs. Otis L. Anderson, K. J. Thomson, and Harry Eagle.

From the British Central Scientific Office- Dr. R. H. S. Thompson.

From the Canadian Army Medical Corps- Lieut. A. H. Neufeld.

The Chairman, Dr. Moore, opened the meeting by reading a statement from Dr. Chester Koefler, Chairman Committee on Chemotherapeutics and Other Agents, concerning the use of penicillin in human syphilis which established the priority of Dr. John F. Mahoney in this field. He also described briefly the results obtained up to the present with penicillin in human beings and experimental animals.

There followed a general discussion of the available clinic material as to

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early syphilis, of the clinic directors present, together with availability of bed space and the adequacy of follow-up. To this were added certain data available from Dr. Herman Bundesen, President Board of Health, Chicago, concerning the Chicago Intensive Treatment Center. These data are as follows:-

	<u>Cases of early syphilis available per month</u>	<u>Bed space available</u>	<u>Adequacy of follow-up</u>
Cox Boston	About 15	10	70 - 80 per cent
Thomas New York	100+	Any necessary number	75 per cent
Schoch Dallas	35	15	75 " "
Barnett San Francisco	25	4	75 " "
Bundesen Chicago	About 50	50	90 " "
Mahoney Stapleton	15	Unlimited	100 " "
U.S. Army Ft. Bragg	About 75	50	100 " "
U.S. Navy Bethesda	25	About 25	100 " "

The clinicians enumerated can provide among them about 350 cases of early syphilis per month with adequate bed space for their study, and with adequate follow up. As to follow-up of cases in the U.S. Public Health Service Venereal Disease Research Laboratory at Stapleton, and in the U.S. Army and Navy centers at Fort Bragg and Bethesda, it was stated that patients could be assigned after hospitalization to duty in the neighborhood, and maintained on such a status for a minimum period of one year, permitting complete follow-up.

It was agreed by all of the clinic directors represented and by Colonel Turner for the Army and Captain Hall and Commander Schwartz for the Navy, that each participating clinic, including those of the Government services, would cooperate in a planned investigation, each clinic utilizing a treatment scheme indicated to it by the steering panel.

There ensued a discussion of several plans of treatment based on a memorandum submitted by the Chairman. It was agreed that at the outset three different treatment schemes would be employed. Each of these held constant a total duration of treatment of eight days and a total number of doses of penicillin of 60, given within the 8-day period at a constant time interval between doses of 3 hours. The dose was to be varied as follows:

<u>Group</u>		<u>Total units of penicillin</u>
I	60 doses of 1,000 units each	60,000
II	60 doses of 5,000 " "	300,000
III	60 doses of 20,000 " "	1,200,000

These dosage levels were chosen on the assumption that the efficacy of a total dosage of 1,200,000 units over an 8-day period had already been tentatively demonstrated by Mahoney's original four cases and by the animal experiments. The varying dosage levels selected permit a five-fold spread and a probable rapid orientation as to the effective dose administered within this 8-day time period and at these three-hour intervals. It was understood that the lower doses might at once prove to be ineffectual, in which case the dosage scheme should be revised by the steering panel.

In view of the possibility that penicillin alone might prove to be less effective than the original observations indicated, and of the possible desirability of the eventual necessity of combining penicillin with another form of treatment, it was further agreed that three additional groups of patients would be studied combining penicillin with mapharsen in subtoxic and presumably subcurative dosage. In view of the lack of certain fundamental information as to the combination of these two drugs, however, it was agreed that the groups in question would not be initiated until it had been demonstrated that (a) mapharsen and penicillin are pharmaceutically compatible; (b) each does not increase the toxicity of the other for experimental animals; and (c) each does not materially reduce the in vitro effect of the other. Dr. Harry Eagle was delegated to provide this information from his laboratory, and states that he can do so within a two week period. Assuming Dr. Eagle's results to show no alteration from the anticipated in these respects, the following treatment groups are to be set up:

<u>Group</u>		<u>Total units of penicillin</u>
IV	Penicillin as in Group I plus Mapharsen 40 mg. daily to a total of 320 mg.	60,000 units
V	Penicillin as in Group II plus mapharsen 40 mg. daily to a total of 320 mg.	300,000 units
VI	Penicillin as in Group III to plus mapharsen 40 mg. daily to a total of 320 mg.	1,200,000 units

The dose of 320 mg. of mapharsen has been chosen as providing within an 8-day period an expected mortality between 1 in 2,000 and 1 in 3,000 patients, and a subcurative effect in an estimated 60 per cent of those treated.

There was some debate as to whether the mapharsen would be administered simultaneously with the penicillin or after, but in the pilot experiment it seemed desirable to administer it daily on the same days as the penicillin treatment was given.

It was agreed that the U.S. Army and Navy, Dr. John F. Mahoney at the Venereal Disease Research Laboratory at the U.S. Marine Hospital, St. Ploton, and Dr. Oscar Cox in Boston would prefer, for the time being at least, to operate on the largest dose schedules since they are dealing with military personnel, including Coast Guard, and since in such personnel it is undesirable to adopt treatment schemes which have as yet not been demonstrated to be of value.

It was agreed that the steering panel would allocate certain of these six treatment systems to the participating clinics.

It was further agreed that the participating clinics, including the U.S. Army and Navy, would utilize duplicate records including any record form desired by the clinic in question, plus a standard record form to be supplied by the steering panel and to be returned to it for statistical evaluation.

It was agreed that the steering panel was authorized to devise such a record form.

It was agreed that all treatment failures on any dosage schedule should be placed on arsenic therapy.

The above conclusions were reached at the morning meeting in which all of the persons enumerated above participated. At the conclusion of this meeting and after luncheon the steering panel met in executive session.

It was felt that the steering panel should be enlarged to include representatives of the U.S. Army in the person of Lt. Col. T. B. Turner, and the U.S. Navy in the person of Comdr. W. H. Schwartz. This action was taken in anticipation of the approval of the Subcommittee on Venereal Diseases.

Also invited to attend the meeting of the steering panel were Doctors Stokes and Cox of the Subcommittee on Venereal Diseases, since the action of this panel must eventually receive the approval of that subcommittee.

During the afternoon session, therefore, the panel met consisting of the following persons:-

Drs. J. E. Moore, J. F. Mahoney, Barry Wood, Jr., Col. Turner, and Comdr. Schwartz, and also present Drs. Cox and Stokes. The panel elected Dr. Moore as Chairman.

The first business of the panel was the selection of clinics to participate in a study of early syphilis. In addition to the clinic directors present and the information presented concerning the Chicago Intensive Treatment Center, applications were also on file, either directly to Dr. Moore or through Dr. Keefer, from Dr. Harold N. Cole, Cleveland, Dr. Loren Shaffer, Detroit, and Dr. A. Benson Cannon, New York.

These latter applications represent in the case of Dr. Cole also Dr. Joseph Wearn and Paul Gyorgy, Cleveland, with whom Dr. Keefer and the Committee on Chemotherapeutics had already made some tentative arrangements; in the case of Dr. Shaffer, Dr. Robert C. Jameson, Wayne University, Detroit, who had requested penicillin from Dr. Keefer; and in the case of Dr. Cannon, Dr. M. H. Dowson, Presbyterian Hospital, New York, who had requisitioned penicillin. Drs. Dawson and Jameson were referred by Dr. Keefer to the Subcommittee on Venereal Diseases.

It was felt by the steering panel that, in view of the available supply of penicillin, the desirability of obtaining certain preliminary pilot information before too wide participation of many clinics, the availability of clinic material from the clinic directors present, and the lack of information on certain points available from Cole, Shaffer, and Cannon, action on the applications of these last three should be postponed temporarily. The Chairman was, meanwhile, authorized to communicate with Drs. Cole, Shaffer, and Cannon for additional information. The steering panel then decided that the following clinic facilities would be asked to undertake a study of early syphilis:-

<u>Clinic</u>	<u>Group of pts. to be studied</u>	<u>Total number of cases available for treatment within 3-month period</u>	<u>Amount of penicillin required per month from OSRD</u>
U.S. Army	III and IV (60 pts. each)	120	None- to be supplied from Army sources
U.S. Navy	III	75	None- to be supplied from Navy sources
Dr. J. F. Mahoney	III	45	18 million units
Dr. Evan Thomas	I and IV	300	6 million units
Dr. Arthur Schoch	II	100	10 million units
Dr. C. W. Barnett	II	75	8 million units
Dr. Oscar Cox	III	40	16 million units
Dr. S. W. Becker			
Chicago Intensive Treatment Center	V	120	12 million units

This allocation of clinics to treatment groups provides for the following approximate number of patients to be treated in each group:-

<u>Groups</u>	<u>Participating clinics</u>	<u>Number of cases</u>
I	Thomas	150
II	Schoch (100) Barnett (75)	Total 175
III	U.S. Army (90) U.S. Navy (75) Mahoney (45) Cox (40)	" 250
IV	Thomas	150
V	U.S. Army (90) Becker, Chicago Intensive Treat.Center (120)	" 210
VI	None for the time being, because of shortage of penicillin	---

As to late syphilis, the steering panel had before it proposals from Drs. J. E. Moore and Charles F. Mohr, Johns Hopkins University (particularly for the treatment of neurosyphilis, including especially acute syphilitic meningitis and early paresis, late gummatous syphilis, and treatment-resistant early syphilis); from Dr. J. H. Stokes, University of Pennsylvania (particularly for the treatment of syphilis in pregnancy, interstitial keratitis, and neurosyphilis); Dr. Paul O'Leary, Mayo Clinic, late syphilis in general; Dr. Walsh McDermott, New York Hospital, late syphilis in general; and Drs. Harry Solomon and H. Houston Merritt, Boston Psychopathic Hospital, general paresis.

It was agreed by the panel that, since no information exists as to how to use penicillin in late syphilis, since it was probable that much larger doses would be necessary than in early syphilis, and since the available supply allocated by the Committee on Chemotherapeutics was 40 million units a month, it would be desirable to limit a study of late syphilis for the time being to the two clinics of Drs. Stokes and Moore, and that 20 million units of penicillin per month should be allocated to each of these clinics.

It appeared to be the sense of the meeting that as promptly as supplies of penicillin permitted, the clinics of Cole, Shaffer, and Cannon should be drawn into the picture for early syphilis, and those of O'Leary, McDermott, and Solomon for late syphilis.

It was agreed by the panel that Dr. Mahoney would draw up a record form for general use in early syphilis; that this form should consist of an original blank to be completed at the end of treatment with subsequent additional blanks to be filled in as follow-up information accumulates. This form drawn up by Dr. Mahoney will be submitted to the members of the steering panel for comment before final adoption. When finally adopted the form will be printed and distributed to clinic directors. Each clinic director, including those from the Army and Navy, will be requested to fill in the forms as indicated and to send them to Dr. Moore, Chairman of the panel, for running statistical analyses.

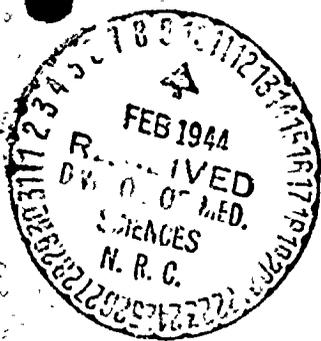
It was agreed that in early syphilis a fundamental feature of the treatment and follow up of patients was serologic testing. In respect of this it was agreed that each clinic would be asked to perform serologic tests at stated intervals utilizing a quantitative test by whatever technique is in current use in that clinic; and that, in addition, each clinic will be furnished with mailing containers by Dr. Mahoney, in which duplicate samples of each blood specimen obtained from each patient are to be sent to Dr. Mahoney's laboratory under Government frank.

Dr. Wood drew attention to the fact that the Committee on Chemotherapeutics had already provided small quantities of penicillin for the treatment of syphilis to the following persons:- Dr. Oscar Cox, Boston, Dr. Barry Wood, St. Louis, Drs. Wearn, Gyurgy and Cole, Cleveland, Drs. Bloomfield and Barnett, San Francisco, and Dr. Francis Blake, New Haven. Dr. Wood felt that Dr. Keefer should be consulted as to the wishes of the Committee on Chemotherapeutics with regard to a continuing supply of penicillin for this purpose to these persons enumerated above who have not been included in the present recommendations of the steering panel already outlined. It is pointed out that Drs. Cox and Barnett are included among the participating clinics selected by the steering panel; that action on Dr. Cole has been temporarily postponed by that panel; and that the panel took no formal action concerning Drs. Wood and Blake.

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Medicine (Venereal Disease)

NATIONAL RESEARCH COUNCIL
Division of Medical Sciences
Acting for
COMMITTEE ON MEDICAL RESEARCH
of the

Office of Scientific Research and Development
Committee on Medicine

SUBCOMMITTEE ON VENEREAL DISEASES

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Minutes of the twentieth meeting of
September 29, 1943.

The twentieth meeting of the Subcommittee on Venereal Diseases, National Research Council, was held at the National Academy of Sciences in Washington on September 29, 1943. Present were the following:

- From the Subcommittee on Venereal Diseases Doctors J. E. Moore, N. A. Nelson, R. D. Herrold, Oscar F. Cox, J. F. Mahoney, Walter Clarke, John H. Stokes.
- From the Committee on Medicine Doctors O. H. P. Pepper and Warfield T. Longcope.
- From the United States Army Lt. Col. T. B. Turner, Lt. Col. R. D. Prentiss, Majors J. P. Scholtz, Thomas H. Sternberg, and James J. Jockson, and Capt. Granville D. Larimore.
- From the United States Navy Comdr. W. H. Schwartz and Comdr. A.J. Peyrera.
- From NRC-CMR Doctors Lewis H. Weed, W. C. Davison, E. H. Cushing, G. W. Guest, T. R. Forbes, G. A. Carden, G. K. Anderson, E. C. Andrus, G. H. Sprague, and Philip Owen.
- From the U. S. Public Health Service, Assistant Surgeon General J. R. Heller, Jr., Doctors Harry Eagle and K. J. Thurman, and Special Consultant William F. Snow.
- From the Office of Civilian Defense Dr. Hamilton Southworth.
- From the Royal Navy Surgeon Comdr. R. W. Mussen
- From the Markle Foundation Mr. Archie S. Woods.

The Chairman opened the meeting with a description of his recent visit to Great Britain for the purpose of study of the venereal disease situation in the British civilian population, the United States Army, and the British Armed Forces.

There was then presented the Minutes of a Conference on biologic false positive serologic tests for syphilis held on July 19. The Chairman reported in addition to the information contained in these Minutes that 705 specimens from the Baltimore American Red Cross Donation Center had been examined in his own laboratory.

These specimens were all from donors originally seronegative who had given multiple donations ranging from 3 to 13 in number. Ten were positive, 99 gave anti-complementary complement fixation tests with negative flocculation tests, 596 were negative. Not all of the 10 positive donors had been examined to determine the presence or absence of syphilis. The Chairman reported, however, that he had seen altogether about 16 persons who had been found to have positive blood tests after multiple donations, of whom roughly three quarters were biologic false positive and one-



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quarter syphilis.

The Chairman further reported that since the July 19 Conference certain experimental work has been done by Major Charles Rein and Lt. Robert Barnard. This work is summarized in a letter dated September 25 from Dr. Herbert Lund, as follows:-

"Dear Doctor Moore:

Dr. Charles Rein, Dr. Robert Barnard and I have discussed the progress of the work on postdonation reagin variation today and the following summarizes the progress so far:

A series of 300 selected initial male donors was studied. Predonation and postdonation tests were made and sample groups were tested starting on the sixth day at daily intervals to the eighteenth day and thereafter at one month and two month intervals after the donation. The samples were tested by the battery used at the Army Medical Center. It can be stated that so far a definite increase in reactions was found following the donation. The peak was reached at the 13th to 15th day but the increased number of reactions persisted for a month. The degree of reactivity attained was in some instances sufficient to give a doubtful or positive reaction by ordinary laboratory tests. The specimens were checked by me and there was a reasonable correlation between the above battery and our technic. This suggests that blood donation may be a factor in the production of weak false positive reactions.

The above experiments should be repeated under more suitable and controlled conditions.

A preliminary experiment performed by Drs. Rein and Barnard suggests that an increase of reagin titer may occur during the actual donation of blood.

The following experiment was proposed by us today and we think that if it is carefully controlled it should give us a definite answer. Dr. Barnard will collect predonation samples from 300 selected initial donors. Each donor will be subjected to three serological examinations: (1) immediately before the donation, (2) immediately after the donation, and (3) at selected intervals following the donation. A control series will be run in the same manner on 300 other non-donors and will consist of only two serological examinations. Tests will be run at the Processing Center under the supervision of Dr. Barnard. Those sera which show any degree of positivity will be sent to Dr. Rein and me for additional studies. The controls will be handled in a similar manner. This study will be carried on for a period of approximately 15 days. The positive reactors, however, will be followed for as long as is indicated.

The following study is proposed to determine the effect of donation on the reactivation of seronegative syphilitics. Twenty seronegative syphilit-

"ics. will be selected by you, ten of which have received their therapy during the preceding 6 to 12 weeks and the other ten of which have received no therapy or their last therapy at least two or three years prior to the experiment. These donors will have a predonation blood specimen taken and additional specimens taken at weekly intervals for a period of ten weeks. These specimens will be subjected to the battery of tests at the Army Medical Center as well as to my technic at City Hospital. This study may throw light on the provocation of reagin resulting from blood donation.

Sincerely yours,

S/ Herbert Lund, M.D.
Pathologist. "

There ensued a general discussion in which it was agreed that the subject was not one of major importance from the standpoint of the Red Cross; that publicity concerning it was absolutely undesirable; but that from the scientific standpoint further study was desirable. The suggestion was made that a further study of the problem be centered in Philadelphia; and that Lt. Barnard be transferred from the Columbus, Ohio, Blood Donation Center to that in Philadelphia. This appears to have three advantages: a) that the donor population in Philadelphia is larger, more stable, and more readily accessible than that in Columbus; (b) a competent clinical consultant in the person of Dr. Stokes is available; and (c) that the processing laboratory of Sharpe and Dohme is located in the immediate vicinity. It was suggested that it might prove to be desirable to establish the study under an OSRD contract with Dr. Stokes as responsible investigator. The Chairman was authorized to communicate with Dr. Stokes and Major Rein to arrange a conference between them for the purpose of considering such a planned study in Philadelphia.

There arose for further discussion in this connection the difficulty which has been experienced by the Duke University group and that of Columbia in obtaining an adequate supply of serum from biologic false positive subjects. The Conference of July 19 had suggested that an experiment be set up with induced malaria in volunteers, possibly chosen from a group of conscientious objectors. It was pointed out that such an experiment involved a risk of life which was probably not justified for the end in view. It was further pointed out, however, that a study for another purpose of induced malaria in syphilitic volunteers is under way at the Goldwater Memorial Hospital in New York under the direction of Dr. James A. Shannon, and that arrangements might be made through Dr. Shannon to obtain suitable blood specimens. It was also suggested that biologic false positive sera from malarious patients might be obtained from U. S. Army sources at the Lederman General Hospital or the Percy Jones Hospital, from certain U.S. Navy hospitals, or from the U.S. Public Health Service Marine Hospital at New River, N.C. It was likewise suggested that biologic false positive specimens from leprosy patients might be obtained from the U.S. Public Health Service Hospital at Carville, La. The Chairman was authorized, after consultation with Major Rein, who had been appointed as chairman of a steering panel by the July 19 Conference, to approach these several possible sources of biologic false positive specimens.

There was then presented the Minutes of a Conference on the Chemical Prophylaxis of Venereal Disease held on September 20 (the Minutes of this Conference have been circularized). Amplifying these minutes is the following report of another small Conference held on September 27th. This report follows:-

Memorandum to Subcommittee on Venereal Diseases

Report of meeting in Baltimore - Monday, September 27, 1943

Present:

Dr. Herbert O. Calvert, Food and Drug Administration, Washington, D.C.
Mr. Geoffrey Woodard, Food and Drug Administration, Washington, D.C.
Dr. Marvin Thompson, Warner Institute
Surgeon Harry Eagle, U.S. Public Health Service
Dr. George O. Doak, U.S. Public Health Service
Dr. Harry G. Steinman, U.S. Public Health Service
Assistant Surgeon Harold J. Magnuson, U.S. Public Health Service

1. On the basis of the data in hand concerning spirocheticidal activity in vitro, systemic toxicity, prophylactic activity in rabbits, and ease of manufacture, the choice of compounds for use in a preliminary human experiment has narrowed down to five (the 4-OCH₂CONH₂, 4-NHCONH₂, 4-CONH₂, 4-SO₂NH₂ and 3-NH-4-OC₂H₄OH phenyl arsenoxides). All have an approximately equal local toxicity on rabbit skin and mucous membranes, and on patch tests in man. The choice among these five compounds will depend in large measure on the availability of intermediates, and the cost of manufacture. Inquiries are now in progress as to the feasibility of commercial production of either intermediates or the final product, in 50 kg. lots.
2. In view of the wide differences effected in the skin arsenic concentration by changing the type of ointment base used, it seems desirable to determine whether there is a correlation between skin arsenic concentration and the prophylactic efficacy of a given arsenical. To that end, the same arsenoxide (4-OCH₂conh₂) will be put up in three ointment bases known to effect widely differing skin arsenic concentrations, and those ointments will be tested for prophylactic efficacy in comparison with solutions in propylene glycol. The ointment bases selected are those resembling As-2017, As-2210 and a petrolatum base.
3. Two compounds selected from the preceding list will be put up in two different ointment bases, at each of two concentrations (0.2 and 0.05 per cent). The bases (one resembling As-2012 and the other to be selected by Doctors Thompson and Calvery on the basis of further studies with the particular arsenoxides to be used), will be of the vanishing cream type. One liter of each of the eight ointments will be prepared, which will be put up in 4 cc. tubes for human use. Those tubes will be subjected by Doctors Calvery and Thompson to the usual stability tests, and the product after testing will be assayed for biological activity in the laboratory of Doctor Eagle. The provision for an adequate number of wax-lined tubes is to be discussed with Major Bambach.

Report- cont'd

4. Since the ointment bases selected are of the vanishing cream type, it is desirable to ascertain the partition coefficient of representative arsenoxides between water and petrolatum, in order to determine its distribution between the water and oil phases of the emulsion. It is also desirable to ascertain the susceptibility of the arsenoxides to oxidation in aqueous solution, and the protective action of e.g., ascorbic acid, in preventing that oxidation. These two studies will be undertaken in the laboratories of Doctor Eagle, using both a biologic and chemical test for the persistence of the original compound.

Since 10 per cent sulfathiazole is to be used in the human experiment, all the ointments discussed in paragraphs 2 and 3 are to include 10 per cent sulfathiazole.

Harry Eagle, Surgeon

U.S. Public Health Service, Venereal Disease Research and Post-graduate Training Center, Johns Hopkins Hospital, Baltimore, Maryland.

On the basis of these reports there ensued general discussion of the subject of chemical prophylaxis in relation to existing and future OSRD contracts. It was agreed that as to chancroid and lymphogranuloma the information in hand seemed to be complete and undesirable of further investigative study. As to gonorrhoea, further information will depend on the outcome of the animal experiments by Drs. Justina Hill and C. Phillip Miller, and the U.S. Public Health Service experiment on human volunteers, the latter of which has just gotten under way. As to syphilis it was agreed that further study of calonei, particularly with regard to the influence of bases, should be continued in Dr. Chesney's laboratory; and that arsenicals should be further studied in the laboratories of Drs. Eagle, Carpenter, and Fleming.

As to granuloma inguinale, the Chairman presented the abstract of a paper by Katherine Anderson, Department of Pathology, Vanderbilt University Medical School, which appeared in SCIENCE 97: 560, June 18, 1943. This paper deals with "The cultivation from granuloma inguinale of a microorganism having the characteristics of Donovan bodies in the yolk sac of chick embryos." The Chairman was authorized to approach Dr. Anderson and Dr. Goodpasture, the Chief of the Department of Pathology, to ask their cooperation in a study of the efficacy of various prophylactic agents in this disease, since these experiments seemed to offer the first hope of knowledge in this direction. It was also agreed that confirmation of Anderson's experiments was desirable and that Dr. Geoffrey Rake should be asked to undertake them.

The use of penicillin in syphilis was then discussed. The available information to date was presented by Drs. Mahoney and Eagle and by the Chairman, who summarized Dr. Rake's prophylactic experiments. It was agreed that the clinical and experimental evidence so far available justified an extensive trial of penicillin in

human beings; and the Subcommittee passed the following three recommendations:-

1) IT IS RECOMMENDED THAT THE UNITED STATES ARMY AND NAVY UNDERTAKE AND/ OR CONTINUE THE EXPERIMENTAL STUDY ON PENICILLIN IN THE TREATMENT OF EARLY SYPHILIS IN MAN. ARRANGEMENTS SHOULD BE MADE TO FOLLOW SUCH PATIENTS CLOSELY FOR A MINIMUM PERIOD OF ONE YEAR.

2) IT IS RECOMMENDED THAT UNDER THE JOINT AUSPICES OF THE COMMITTEE ON CHEMOTHERAPEUTICS AND OTHER AGENTS AND THE SUBCOMMITTEE ON VENEREAL DISEASES A MAXIMUM OF EIGHT PARTICIPATING CLINICS (EXCLUSIVE OF THE U.S. PUBLIC HEALTH SERVICE VENEREAL DISEASE RESEARCH LABORATORY AT STAPLETON, STATEN ISLAND)* BE INVITED TO STUDY THE EFFECT OF PENICILLIN IN SYPHILIS. THESE CLINICS AND THE TYPE OF SYPHILITIC INFECTION TO BE STUDIED ARE AS FOLLOWS:-

LELAND STANFORD JUNIOR UNIVERSITY (DR. C. W. BARNETT) EARLY SYPHILIS
BOSTON UNIVERSITY (DR. OSCAR COX) EARLY SYPHILIS
NEW YORK UNIVERSITY (DR. EVAN W. THOMAS) EARLY SYPHILIS
DALLAS SYPHILIS AND VENEREAL DISEASE CLINIC (DR. ARTHUR SCHOCH) EARLY SYPHILIS
UNIVERSITY OF PENNSYLVANIA (DR. JOHN H. STOKES) EARLY SYPHILIS, SYPHILIS IN PREGNANCY, AND CONGENITAL SYPHILIS, ESPECIALLY INTERSTITIAL KERATITIS
CORNELL UNIVERSITY (DRS. BRUCE WEBSTER AND WALSH McDERMOTT) LATE SYPHILIS
JOHNS HOPKINS UNIVERSITY (DRS. J.E.MOORE AND C.F.MOHR) LATE SYPHILIS.

3) IT IS RECOMMENDED THAT A PANEL BE ESTABLISHED CONSISTING OF THE CHAIRMAN COMMITTEE ON CHEMOTHERAPEUTICS AND OTHER AGENTS AND TWO MEMBERS OF THE SUBCOMMITTEE ON VENEREAL DISEASES (DRS. J.E.MOORE AND J.F.M AHONEY) TO SUPERVISE AND COLLATE THE INFORMATION FROM THE PARTICIPATING CLINICS ENUMERATED ABOVE. A CONFERENCE OF THIS PANEL WITH THE CLINIC DIRECTORS SELECTED SHOULD BE HELD IN THE NEAR FUTURE.

With regard to the use of penicillin in gonorrhea, Major Sternberg reported that about a thousand cases had now been treated by the U.S. Army. In sulfonamide-resistant gonorrhea the effective dosage range was found to be 80,000 to 120,000 units in 15 hours. However, it was also found that after a total of 40,000 given in 10,000 unit doses every 3 hours, 90 per cent of the patients responded. This latter treatment system is currently recommended for Army usage because of the shortage of penicillin. In 12 cases which had originally failed on penicillin it has been found that 10,000 units hourly for 12 hours is curative. Of 600 cases in which reactions are known, there have been only two mild fevers and one unimportant skin rash. Major Sternberg felt that the time-dose relationship in gonorrhea required further study. Dr. Pepper added to the discussion the statement that rashes are beginning to appear in various severe infections treated with penicillin and that these are usually itching, urticarial, or erythema multiforme-like in type. Fifteen such cases have been observed at the University of Pennsylvania.

* The U.S. Public Health Service Venereal Disease Research Laboratory is not included in the above list because this laboratory proposes to manufacture its own penicillin and will therefore be independent so far as the supply is concerned, of the Committee on Chemotherapeutics.

The Subcommittee considered a proposal for OSRD contract from the Johns Hopkins University (responsible investigators Drs. J.E. Moore and C.F. Mohr) on the subject of "The Effect of Penicillin in Syphilis, Especially Late Syphilis". This proposal was accepted and rated "A" with the proviso that if the supplies of penicillin are insufficient to sustain the entire eight clinic program, the amount of penicillin allocated under this grant shall be on a share and share-alike basis with the other clinics. ✓

The Subcommittee then considered an informal suggestion from Dr. Arthur Schoch that he undertake on the basis of an OSRD contract a study of the effect of bismuth ethyl camphorate in man. The Subcommittee agreed that this proposal did not hold particular promise and the Chairman was authorized to communicate with Dr. Schoch to this effect. ✓

A proposal for renewal of contract by Drs. Dan Moore and Elvin Kabat of Columbia University for a "Further Study of Biologic False Positive Serologic Tests" was rejected. ✓

Dr. Harry Eagle reported that by the authority of the Committee on Gas Casualties he had been authorized to prepare for distribution BAL for systemic use in cases of serious systemic arsenic poisoning arising in the course of treatment for syphilis. BAL has been prepared in a relatively stable solution in five per cent concentration in peanut oil and benzyl benzoate. Administered systemically this preparation has shown a striking effect in arsenic poisoning in animals. Thirty pounds of the compound have been turned over by the Army to Dr. Eagle and the material has been distributed to all clinics in the United States utilizing intensive arsenotherapy. The compound may not be used concurrently with antisyphilitic treatment in an effort to avoid arsenic toxicity, since it also does away with therapeutic efficacy. ✓

Dr. Russell Herrold then presented for the information of the Subcommittee some work of his own dealing with the treatment of patients with sulfonamide-resistant gonorrhoea by means of the simultaneous administration of sulfonamides and "denatured" vaccines prepared from viable organisms. By "denatured" Dr. Herrold means that the vaccines are prepared in salt solution without added antiseptics. He has treated about 12 patients and in 6 or 7 of them has obtained startling results. It was pointed out to Dr. Herrold that similar experiments had been conducted by Dr. Alfred Cohn, with whom he was advised to communicate. ✓

The meeting then adjourned.

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NATIONAL RESEARCH COUNCIL
(Venereal Disease)



NATIONAL RESEARCH COUNCIL
Division of Medical Sciences
Acting for
COMMITTEE ON MEDICAL RESEARCH
of the
Office of Scientific Research and Development
Committee on Medicine
SUBCOMMITTEE ON VENEREAL DISEASES
Minutes of the nineteenth meeting of
June 10, 1943.

On June 10, 1943, there was held at the National Academy of Sciences the nineteenth meeting of the Subcommittee on Venereal Diseases. Present were the following:

From the Subcommittee on Venereal Diseases Doctors Moore (Chairman), Stokes, Cox, Nelson, Herrold, and Mahoney,
From NRC-CMR Doctors Cushing, Forbes, Guest, and Carden;
From the U. S. Army Major Sternberg;
From the U. S. Navy Capt. H. H. Montgomery and Licut. Shrouts,
From the U.S. Public Health Service Doctors Vonderlehr and J. R. Heller;
From the Medical Research Council of Great Britain Dr. J. H. Burn;
From TWA Dr. R. B. Miller (National Airport, Washington, D.C.).

The Subcommittee considered six recommendations made by a Conference on intensive arsenotherapy of early syphilis held on May 19, 1943. Those recommendations intended for the Surgeons General, U. S. Army and Navy are included in the minutes of that Conference which have already been circularized and are not herewith repeated. The first, second, fifth, and sixth of these recommendations were approved by the Subcommittee without amendment.

The third recommendation was amended so that its first line reads:
"It is hoped that the U. S. Public Health Service will amplify a statistical evaluation," etc., etc.

The fourth recommendation was approved subject to a qualification that the National Research Council review the propriety of the language of this recommendation, rephrasing it if such rephrasing appears to be desirable.

The Subcommittee then considered the Appendix to the Minutes of the Conference on the Massive Arsenotherapy of Early Syphilis which consists of a tentative draft of a Circular Letter entitled, "The Intensive Arsenotherapy of Early Syphilis. Description of Methods." With minor amendments which have been added to the original copy of this appendix which has already been circularized with the Minutes of the Conference on Intensive Arsenotherapy, the appendix was approved for transmission to the Surgeons General U. S. Army and Navy

The Subcommittee then considered a request from Commander T. J. Carter, Officer in Charge Division of Preventive Medicine, Bureau of Medicine and Surgery, U. S. Navy, through Lt. Comdr. W. H. Schwartz (MC) U.S.N., asking for information on the following points:-

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1. Criteria for adequacy of treatment for syphilis.
2. Discussion regarding the prognostic significance of secondary and serological relapses.
3. Significance of sero-positivity after treatment which was begun during early syphilis.

In respect of these enquiries the Subcommittee, after making certain amendments, approved for transmission to the Surgeon General U. S. Navy a memorandum prepared by Dr. John H. Stokes. This memorandum in the form of a letter to the Surgeon General is herewith appended as Appendix "A".

The Subcommittee then considered certain requests from Lieut. Col. T. B. Turner, Venereal Disease Control Branch, Division of Preventive Medicine, Surgeon General's Office, U. S. Army, with respect to the provisions of Circular Letter 74 regarding the diagnosis and treatment of gonorrhea. The questions proposed by Colonel Turner and the Subcommittee's replies are appended herewith in the form of a tentative letter to the Surgeon General, U. S. Army, as Appendix "B". This appendix also includes an additional recommendation of the Subcommittee.

The Subcommittee then considered a memorandum of the Chairman on the subject of chemical prophylaxis. He reported a recent conference with Lieut. Col. T. B. Turner and others indicating the desirability of an immediate field trial by the U. S. Army of a single tube prophylactic treatment containing 15 per cent sodium sulfathiazole and 30 per cent calomel. Arrangements to determine the optimum base for the inclusion of these two ingredients are under way through Doctors Calvery and Thompson. In this conference with Colonel Turner it was brought out that the laboratory information concerning calomel, together with 35 years' clinical experience with it, was adequate to permit the continuation of the use of this drug without further and detailed laboratory studies, however desirable these latter might be in the determination of certain as yet unclear points. On the other hand, information concerning the prophylactic efficacy of arsenic in syphilis and other venereal diseases should, in the opinion of Colonel Turner and those with whom he conferred, be pushed as promptly as possible. For this reason the Chairman proposed that he be authorized to discuss with Dr. W. L. Flening, University of North Carolina, and with Drs. Charles M. Carpenter and Stafford L. Warren, University of Rochester, a redirection of their experimental approach in chemical prophylaxis to transfer their proposed immediate future studies from mercury to arsenic. This authorization was granted by the Subcommittee.

The Chairman then reported on the status of certain proposals for contract, original, supplemental, or extension. These were as follows:-

A proposal for extension of contract by Doctors Kline and Lankelma of Cleveland has been withdrawn by them on the ground that draft deferment for a chemist could not be absolutely promised, nor could arrangements be made to extend the contract for a three year period.

Two proposals from the University of Rochester by Doctors Warren and Hodge, and Warren and Steadman, respectively, have been withdrawn because of the transfer

of Hodge and Steadman to other work.

A proposal for supplemental contract in the amount of \$500/1250 by Dr. W. L. Fleming, University of North Carolina, to permit the installation of an air conditioning apparatus in his experimental syphilis laboratory was approved by the Subcommittee and rated "A".

A proposal for extension of contract for a period of one year by Dr. Justina Hill, Johns Hopkins University, for a continued study of the establishment of a gonococcal infection in experimental animals by methods applicable to the study of venereal disease, in the amount of \$9,170, was approved by the Subcommittee and rated "A".

A proposal for extension of contract for a period of one year by Dr. Herbert Lund, Western Reserve University, for continued investigation of biologic false positive reactions in the serology of syphilis in the amount of \$6300. was approved by the Subcommittee and rated "A".

The Chairman then brought up for discussion a proposal by himself representing the Johns Hopkins University, in collaboration with Dr. Reuben Kahn, University of Michigan. This proposal for contract is not yet formally completed but the Chairman requested consideration of it prior to its formal submission. After explaining the nature of the proposed work the Chairman left the room and the matter was discussed under the temporary chairmanship of Dr. John H. Stokes. The Subcommittee was unwilling to give its approval in advance of submission of the proposal for contract and raised a number of issues concerning the desirability of the proposed work. It was pointed out that Major Charles Rein, U.S. Army Medical School, has already demonstrated that the new Kahn verification test is of no value, and that he has developed a verification test of his own which appears to solve the problem of differentiation between true positive tests in syphilis and biologic false positive tests. The Chairman and proposer, Dr. Moore, was therefore directed, when the proposal for contract has been completed in its final form, to circulate it among the members of the Subcommittee, together with covering letters from Major Rein and from Dr. Harry Eagle indicating their opinions of the desirability of the proposed outline of procedure.

The meeting then adjourned.

Surgeon General,
United States Navy,
Washington, D.C.

Sir:

A request having been received from Commander T. J. Carter through Lieutenant Commander William H. Schwartz (MC) USN, for the expression of opinion from the Subcommittee on Venereal Diseases of the National Research Council relative to certain matters regarding the treatment of syphilis, the following group of statements has been prepared.

QUESTION I "Criteria for Adequacy of Treatment for Early Syphilis". The answer to this question depends fundamentally upon the definition of "adequacy". If by adequacy is meant the securing of a condition of noninfectiousness in an infectious case, one kind of answer will be appropriate; if adequacy is to be interpreted in terms of clinical or of radical cure, another answer will be appropriate; if adequacy means the placing of an infected individual at one or another type or stage of involvement in syphilis on a symptomatic status that will permit of full or limited service in the armed forces, still another answer is necessary. The subject is dealt with under each of these three heads briefly as follows:

Treatment to Noninfectiousness. The immediate infectiousness of surface lesions of syphilis is controlled in all but the rare treatment-resistant or arsenic-fast case, so called, by the first one, or at most, two, injections of an effective trivalent arsenical, provided the dose is adequate (0.3 to 0.5 gram arsphenamine 606, 0.4 to 0.6 gram nearsphenamine; 40 to 60 milligrams napharsen). The duration of this effect of one or two injections is not precisely known, but is estimated roughly as approximately thirty to ninety days. Failure to continue treatment does not necessarily, but may in a percentage of cases ranging from 0 to 64%, lead to infectious relapse. A useful tabulation from Cooperative Clinical Group and University of Pennsylvania material is herewith presented:

<u>Arsenical treatment alone</u>	<u>Infectious relapse</u>	<u>Additional heavy metal</u>	<u>Infectious relapse</u>
1- 4 injections	64 percent	20 injections **	45 percent
5- 9 injections	14 percent	20 injections	9 percent
10-19 injections	---	20 injections	4 percent
20-29 injections	---	20 or more injections	3.6 percent
28.8 injections	---	28.2 or more injections	0 percent
30-40 injections	---	"appropriate"	1.2 percent

* University of Pennsylvania figures; all others C.C.G.
** One week of mercurial injections equals 1 injection.

From this tabulation it will be apparent that the critical point at which sharp reduction in the probability of recurrent infectiousness takes place is between the fifth and ninth injections of the arsenical (14% without and 9% with heavy metal) ;

and that the so-called 20-20 standard, often quoted as adequate for treatment to noninfectiousness, reduces the risk of infectious relapse to 4%, beyond which a slow reduction to 0 to 1.2% is secured by prolonging treatment beyond 30 arsenical injections with 30 or more injections of heavy metal.

It will presently be apparent therefore that the best treatment to secure non-infectiousness is practically identical with the optimum treatment for the securing of "satisfactory results" or "cure".

Heavy metal, in the statistical table presented above, is taken to represent 0.2 gram of an insoluble bismuth salt of not less than 57% metallic content, or one week of mercurial inunctions, or its intramuscular equivalent in a water soluble or insoluble mercurial salt.

Adequacy with Respect to "Cure" or "Satisfactory Results". Information on this subject is based on case material observed for not less than two, and upward to twenty, years since the onset of the infection or the institution of treatment. Material of less than two years of observational control is fundamentally weak in its demonstration of the possibility of relapse, since the first two years of infection are overwhelmingly those of relapse predisposition. On adequacy in the sense of "satisfactory results", five groups of data will be quoted (a) Cooperative Clinical Group results in the treatment of early syphilis by a continuous alternating use of arsenical and heavy metal without rest periods, through sixty-five weeks of treatment observation; (b) Johns Hopkins Hospital Syphilis Clinic (Padgett spokesman) reporting on 551 patients completely reexamined five years or more after the termination of their original treatment for early syphilis; (c) optimal treatment for early syphilis, one to twenty years' observation, Cannon reporting; (d) a shortened 20-week system, Hood reporting on Johns Hopkins Hospital material; (e) the 5-day intensive intravenous drip arsenotherapy of syphilis (without the use of heavy metal), Leifer, Chargin and Hyman, 1941, and Elliott, Baehr, Shaffer, Usher and Lough, 1941.

It is not possible at this time to offer more than tentative estimates on 10-day multiple syringe and 10 to 12-week intensive napharsen-bismuth (Eagle-Hogden) systems which are under study, or on the 21-week Army system of Circular Letter 74.

The Cooperative Clinical Group's standard treatment system experience indicates that for satisfactory results, treatment must be continuous and not intermittent or irregular, and must combine the alternate use of an effective arsenical (napharsen is not represented in this material) and bismuth. Striking reductions in effectiveness with occurrence of infectious relapse, progression of syphilitic manifestations, serologic relapse and seroresistance occur in all phases of early syphilis in which intermittence or irregularity is allowed to occur. Disregarding the precise system of administration, the highest proportion of satisfactory results in seropositive primary syphilis was obtained with 10 to 19 injections of arsphenamine with accompanying heavy metal; in seropositive primary syphilis, with 25 to 35 injections; in early secondary syphilis (seen in the first year) 20 to 29 injections. Higher rather than lower dosage of the arsphenamine is recommended. Failure to secure a satisfactory result by 20 injections or less may be met by 10 additional injections,

plus heavy metal, which may double the proportion of unsatisfactory outcomes reclaimed. The irreducible margin of failure in the treatment of early syphilis by older standards ranges from 4% to 27%, depending on method, stage at which treatment begins, adequacy of treatment during the first two years of the infection.

Johns Hopkins Syphilis Clinic, Padgett reporting on a particularly valuable material because of the length of observation (over 10 years in half the patients), showed clearly the importance to adequacy of the treatment result of the stage at which treatment is begun (82% cure in seronegative primary syphilis, 68.8% in secondary syphilis; 58.7% in early latent syphilis). The poorest results, as in the Cooperative Clinical Group series were observed among patients whose treatment was begun in the seropositive primary stage. Cure was obtained by 83.5% of the patients whose treatment during the first six months was by a continuous system, and is increased to 90.4% if treatment during the next six months was likewise continuous. It was shown that the final or "adequate" outcome depended in a directly quantitative fashion not only on the number of doses of the arsphenamine received, but also inversely upon the time span during which it was given. In other words, the more injections in the shorter time, the better the results. The development of early or intermediate relapse was found to be of grave prognostic significance. (See next question.)

Cannon found in a series of six hundred-odd patients treated with three standard arsphenamines, that arsphenamine 606 was incontrovertibly superior to neoarsphenamine or silver arsphenamine, and that one year of regular and continuous treatment with the arsenical injections closely spaced (two-to three-day intervals in the first three to five weeks, and at intervals of not less than one week thereafter) gave the highest proportion of satisfactory results. The difference between seronegative primary, seropositive primary, and secondary syphilis was not more than 6%.

A 20-20 Arsenical-Bismuth Simultaneous Injection Course, Hood Reporting. This shortened system, not comparable because of longer intervals (weekly) with the 26-week system of Army Circular Letter #74, utilizes weekly injections of napharsen and simultaneous weekly intramuscular injections of an oil-suspended bismuth salt. The maximum period of observation (33 months) was only sufficient to indicate that the proportion of unsatisfactory results in the form of seroresistance, sero-relapse, clinical relapse, and involvement of the central nervous system, amounting to 13.6% of the observed series, was approximately that of unsatisfactory results obtained in early syphilis treated with other arsenical drugs and treatment systems. If confirmed by longer observation, such a treatment system should show how little rather than how much treatment is necessary to produce the average or so-called "standard" results which are so strikingly uniform throughout the entire range from 5-day intravenous drip to 65-week continuous combined therapy.

An important contribution of the Eagle-Hogan experimental work on toxicity and therapeutic effect in an exclusively arsenical system for the treatment of syphilis, has been the apparent demonstration that a total dose approximating 20 mg. of napharsen per kilo in man, giving an approximation of 1200 to 1500 mg. total dose, is curative in a high percentage of persons with early syphilis. The time-toxicity relationships are important, the toxicity increasing with the shortening of the time

within which the total dose is administered. It is possible, therefore, to devise a number of systems, of which the present 12-week Eagle-Hogan system is an example, which will secure greatly increased intensity without excessive or impractical increase in toxicity. Another interesting demonstration of an already-recognized fact is the proof that bismuth employed in any and all arsenical systems greatly steps up efficiency. A recent estimate by Eagle rates the increase of efficiency of a 12-week system, under the addition of weekly bismuth subsalicylate injections to the schedule, as approximately 8 times. These principles, important as they are to the interpretation of adequacy, are still under investigation and massive statistics based on treated and "cured" cases will not be available for 12-18 months.

Massive Dose Arsenotherapy ("5-day drip"). The two series, Leifer et al, and Elliott et al, the former with of course the longer series of observed cases, illustrate the following principles regarding adequacy:

- (a) Curative results can be obtained with a trivalent arsenical along (neocarsphenamine, napharsen).
- (b) Of the two, napharsen, because of its low reactivity, is the drug of choice, and 1200 mg. administered in 5 days, the optimum dose.
- (c) In seronegative primary syphilis, 90% to 100% pursue a satisfactory and uneventful course; without reference to type of drug or stage of disease, an aggregate of 81% secured a satisfactory result in one 5-day course; and one re-treatment in 15 cases raised the result to approximately 88% for the entire series (Leifer et al). Elliott and co-workers estimated their curative results at at least 85% of all cases with early syphilis.

Adequacy of Treatment from the Standpoint of Service in the Armed Forces. On this question the Subcommittee on Venereal Diseases of the National Research Council has already offered a tentative basis for evaluation in proposing a scheme of standards for admission of registrants with syphilis to the United States Army. This memorandum, originally included in Selective Service M.R. 1-9, with minor amendments by the Subcommittee on Venereal Diseases, is as follows:-

SUGGESTED SCHEME OF STANDARDS FOR ADMISSION OF REGISTRANTS WITH SYPHILIS

Registrants with (1) confirmed positive serologic tests for syphilis and no clinical manifestations of the disease; or (a) with convincing histories of a trustworthy diagnosis of syphilis; or (3) of treatment for the disease on serologic or clinical grounds even though such evidence may possibly have been inadequate, may be considered for unlimited military service --

- (a) Provided that a negative spinal fluid since treatment was begun has been reported from a trustworthy source; and
- (b) Provided that in infections estimated to be of less than 4 years' duration, at least 30 to 40 arsenical and 40 to 60 insoluble bismuth injections or its equivalent, with a minimum total of 75 injections, have been given, with approximate continuity (no rest periods or lapses) during the first 30 weeks of treatment; and

- (c) Provided that except as further qualified below, in infections estimated to be of over 4 years' duration, at least 20 arsenical injections and 40 to 60 insoluble bismuth injections or its equivalent, with a minimum total of 60 injections have been given in alternating courses; rest periods between consecutive courses not exceeding 8 weeks, being allowable; and
- (d) Provided that in early syphilis and late latent syphilis, as alternatives to the amount of treatment outlined in paragraphs (b) and (c) above, treatment has been given by the Army 26-week system or its equivalent, including a minimum of 40 doses of napharsen and 16 of bismuth; and
- (e) Provided that in early syphilis the patient has been treated with any of the currently accepted systems of intensive arsenotherapy, with or without added fever therapy.

Evidence of duration of the infection shall be weighed by the examiner with due regard for age, general venereal history, and medical guidance of the registrant.

In infections of unknown duration it shall be presumed for classification purposes that those of registrants under 26 years of age are of less than 4 years' duration, and over 26 years, of more than 4 years' duration.

In congenital infections and in acquired infections of more than 10 years' known duration, in which no clinical progression occurred since treatment was begun; and in which a normal spinal fluid has been recorded at some time after treatment was begun, and a negative physical examination recorded not less than 2 years after treatment was terminated, the infection shall be regarded as "quiescent", and the registrant eligible for unlimited military service, provided the treatment in question shall have included 20 arsenical and 20 heavy metal injections.

For the determination of treatment, the signed statements of acceptable treatment sources administering it with total number of doses of each drug and approximate calendar dates of administration and available laboratory and clinical data shall be required as evidence.

QUESTION II. Discussion Regarding the Prognostic Significance of Secondary and Serologic Relapse. The following principles, based in the main upon the groups of material cited in connection with Question I, are widely accepted. Early evidence of potentially unfavorable or relapsing course in an early syphilitic infection can be found in (a) failure of the primary or secondary lesions to heal under an arsenical therapy; (b) continued presence of Spirochaeta pallida in the lesions after the employment of a known effective trivalent arsenical (these two groups constitute treatment resistant syphilis); (c) prematurely early reversal of a positive serologic reaction on the blood to negative (fourth to seventh week in seropositive primary or secondary syphilis); (d) failure of a positive serologic reaction on the blood to reverse to negative after the sixteenth week (in the intensive or five-day drip system reversal is ordinarily expected by quantitative tests between the tenth and eighteenth weeks after the institution of treatment but late secondaries may not reverse for many months, even though "cured").

Cooperative Clinical Group results (Stokes and co-workers) (observation period too short) showed a relapse expectancy of 19.7% including all forms, of which, when observed for more than six months, 12.1% was mucocutaneous, 3.4% asymptomatic neurosyphilis, 4.1% symptomatic neurosyphilis, and 0.9% cardiovascular syphilis.

The unfavorable prognostic significance of early and intermediate relapse was well brought out in Padget's series in which "cure" was achieved in 73.2% of 456 patients in whom no relapse was observed, whereas only 28.2% of those sustaining an intermediate relapse achieved cure. Persistent seropositive reactions on the blood, however, occurred in 16% of those who sustained no relapse, and in 10.3% of those who underwent intermediate relapse. Late benign syphilis developed 8 times as frequently in relapsers as in nonrelapsers, cardiovascular syphilis 3.5 times as frequently; neurosyphilis 6 times as frequently; multiple late manifestations 7.5 times as frequently in relapsers as in nonrelapsers. The significance of weak positive serologic reactions on the blood occurring in the course of a series of negatives in treated early syphilis have been emphasized as of relapse significance by certain authors.

QUESTION III. Significance of Seropositivity after Treatment which was Begun during Early Syphilis. Certain aspects of relapsing and persistent seropositivity after treatment begun in early syphilis have been indicated above. Broadly speaking, Padget's experience indicated that a residue of 14.9% persistent serologic positiveness would appear in a series of early syphilitics on whom the satisfactory clinical results he described had been secured. In those cases there would be no manifestations such as abnormal spinal fluid, cardiovascular disease, visceral disease, and so forth, to accompany the persistent seropositivity. Broadly speaking, persistence of a positive serologic reaction on the blood of early syphilitics under treatment by the older standard continuous systems is an indication of presence of asymptomatic neurosyphilis, and calls for an examination of the spinal fluid immediately. The more intensive foreshortened treatment systems seem so materially to have reduced the likelihood of the occurrence of asymptomatic neurosyphilis that the neurosyphilitic significance of persistent seropositivity will probably be greatly reduced by their use. In addition to asymptomatic neurosyphilis, syphilis of the cardiovascular system, often coming to recognition five or more years after the cessation of treatment, may be included in the prognostic significance of seropositivity of a persistent type in early syphilis, but this is definitely less important than neurosyphilis. Moore and Padget in their analysis of seroresistant syphilis (early) emphasize the seriousness of seroresistance in early syphilis and its relatively lesser significance in late syphilis. Twenty-three percent of their seroresistant group sustained infectious relapse as against 5% who secured prompt serologic reversal. Neurosyphilis occurs in 31% of the seroresistant cases, but in only 18% of those who sustain prompt reversal.

Adequacy of Treatment for Late Latent Syphilis (2 years' duration or longer) The data presented (Discker, Clark, and Moore) in a study of 926 patients with latent syphilis followed for 5 years or longer indicate that

- (a) Latent syphilitics do very well, regardless of the type and amount of

treatment received.

(b) The optimum amount of treatment to reduce progression to a minimum is approximately 20 injections each of an arsenical and a heavy metal.

(c) The over-all rate of clinical "cure" with optimum treatment is about 95%.

(d) Clinical and serologic "cure" in latent syphilis have no relationship.

Adequacy of Treatment for Various Forms of Late Syphilis. Since adequate treatment for late syphilis must be individualized in accordance with the particular case problem, no general formulation is possible.

Respectfully submitted,

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APPENDIX "B"

Surgeon General
United States Army
War Department
Washington, D.C.

Sir:

The Subcommittee on Venereal Diseases has been requested to answer certain questions dealing with the diagnosis and treatment of gonorrhoea, as outlined in SGO Circular Letter No. 74. These questions and the answers of the Subcommittee thereto follow:-

QUESTION 1. Can the requirements of paragraph 3-g, Circular Letter No. 74, dealing with determination of cure in the male (uncomplicated case) be relaxed? It is believed that the criteria of cure required in this paragraph are unnecessarily excessive from the Army viewpoint.

ANSWER: Yes.

QUESTION 2. Can prostatic massage be completely eliminated in the uncomplicated case? Army experience indicates that massage done routinely by inexperienced physicians predisposes to complications.

ANSWER. Yes.

In explanation of the affirmative answers to Questions 1 and 2 above the Subcommittee believes that an adequate test of cure in cases that become symptom-free during the first week may be limited to clinical observation for three subsequent weeks. If there is no clinical relapse, such patients may be considered cured. Prostatic massage is not necessary. It is therefore recommended that paragraph 3-g, Circular Letter No. 74, be revised to read as follows:-

"Patients who have a clear urine, no urethral discharge, and no other clinical evidence of gonococcal infection, by the end of the 5th day of treatment with sulfathiazole or sulfadiazine should be observed once a week for three weeks. Such observation should determine the presence or absence of urethral discharge and of pus in the urine. If these examinations are consistently negative, the patient may be discharged as cured. Prostatic massage should not be done."

It is also recommended that the second sentence in paragraph 3-h (1) of Circular Letter No. 74 be deleted. The sentence desirable of deletion reads as follows:- "The prostatic secretion should be included in the study of all types of infection"

QUESTION 3. Is the recommended dosage of sulfathiazole (4 gr. daily for 5 days) still considered the optimal treatment for gonorrhoea?

ANSWER. Yes.

QUESTION 4. In view of the known rapid excretion of sulfathiazole, would it be desirable to shorten the interval between courses from five days to two to three days? This would be advantageous in saving a number of non-effective days.

ANSWER. Yes.

QUESTION 5. Is the Section on the diagnosis and treatment of gonorrhea in the female adequate; and if not, what revisions are suggested?

ANSWER. No. It is recommended that the section of Circular Letter No. 74 dealing with diagnosis in the female be amended as follows:-

Paragraph 3-b should be replaced by the following

"(1) A diagnosis of gonorrhea must not be made in the absence of laboratory confirmation. If treatment is to be given immediately and before laboratory confirmation is available (see 3-e (2) (g)), specimens for smear and/or culture should be obtained before treatment is begun, for subsequent laboratory study.

"(2) The detection of gram-negative, intracellular diplococci in smears, or of organisms characteristic of the gonococcus in cultures, confirms the diagnosis of gonococcal infection. (Caution: The normal genital bacterial flora, and the flora of nonspecific infections of the female genitalia, may contain organisms which, in smear, closely resemble gonococci. Cultural methods should be utilized, therefore, whenever available.) In competent hands, cultures are also of particular value in cases in which no gonococci can be found in smears.

"(3) Specimens for smear or culture may be obtained from urethral exudate (if any); from the para-urethral (Skene's) glands after thorough stripping; from the cervical canal, after thorough cleansing of the cervix and squeezing it between the blades of a bivalve speculum; or from the vulvo-vaginal (Bartholin) glands or the rectum, if clinical evidence of infection is present in the two latter areas."

In paragraph 3-e (2) (c) the last sentence should be changed to read as follows:

"There should, however, be a lapse of two or three days between the courses of medication. "

It is also recommended that paragraph 3-b (1), second sentence, which reads: "Treatment for gonorrhea should be started at once in women who have evidence of this disease, even though laboratory studies are negative or not available," be deleted and that the following be inserted after 3-e (2) (f), and marked "(g)":

"The treatment of females should be begun at once with or without laboratory confirmation of the diagnosis, if the history and/or the clinical evidence

The Surgeon General -

indicate that infection is likely to have occurred. Prompt treatment in every such case will prevent or check pelvic invasion in most cases. Grounds for suspicion that infection has occurred are as follows:

"(1) History of a recent sex contact with an infected person. Treatment will serve as delayed prophylaxis or as early treatment.

"(2) Confirmed history that a sex contact of the patient has subsequently acquired gonorrhea.

"(3) A history of a sex contact followed by suggestive signs or symptoms of gonococcal infection that cannot otherwise be accounted for."

In consideration of these suggested revisions Dr. John F. Mahoney submitted a letter under date of May 19 dealing with the questions important from the military standpoint of the administrative, therapeutic, and epidemiologic management of patients with practically certain gonococcal infection in whom, however, bacteriologic proof is lacking. Included among such patients are a considerable number of males with so-called nonspecific urethritis, and likewise a considerable number of females. Dr. Mahoney's suggestions in this respect impress the Subcommittee as so valuable that the following recommendation was agreed to:

THAT THE SUBCOMMITTEE ON VENEREAL DISEASES SUGGESTS TO THE SURGEON GENERAL U.S. ARMY (ATTENTION VENEREAL DISEASE CONTROL BRANCH, DIVISION OF PREVENTIVE MEDICINE) THAT CIRCULAR LETTERS NOS. 74 AND 32 BE REVIEWED BY THE SUBCOMMITTEE ON VENEREAL DISEASES WITH THE IDEA IN MIND OF COMPLETE REVISION, IN ACCORDANCE WITH THE PHILOSOPHY EXPRESSED IN DR. MAHONEY'S LETTER OF MAY 19, 1943.

Respectfully submitted,

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Indexed
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Medicine
(Venereal Disease)

NATIONAL RESEARCH COUNCIL
Division of Medical Sciences
acting for
COMMITTEE ON MEDICAL RESEARCH
of the
Office of Scientific Research and Development
Committee on Medicine
SUBCOMMITTEE ON VENEREAL DISEASES
Minutes of the eighteenth Meeting of
April 7, 1943.

~~CONFIDENTIAL~~

The eighteenth meeting of the Subcommittee on Venereal Diseases was held at the National Academy of Sciences in Washington on April 7, 1943.

Members of the Subcommittee present were: Dr. J. E. Moore, Chairman, Drs. Walter Clarke, Russell D. Herrold, Nels A. Nelson, Oscar F. Cox, John H. Stokes, and John F. Mahoney. Also present from the National Research Council were Drs. Lewis H. Weed, T. R. Forbes, and G. M. Guist; from the U. S. Army Lt. Col. R. A. Prentiss, Jr., Lt. Col. Thomas B. Turner, Major Thomas L. Sternberg, Major Charles R. Rein, and Lt. A. C. Hollister, Jr.; from the U. S. Navy Lt. Comdr. W. H. Schwartz, Lt. Comdr. Ben Klotz, Lt. J. F. Shronts, Ensign Howard Ennes; from Selective Service Col. Richard H. Eanes; from the U. S. Public Health Service Dr. N. B. Hon and Dr. Harry Eagle, from the Veterans' Administration Drs. J. N. Wilson and Hugo Molla; from the Bureau of the Census Dr. Halbert L. Dunn; from the International Health Division of the Rockefeller Foundation Dr. Hugo Muench.

I. The Subcommittee considered a letter from Dr. Charles M. Griffith, Medical Director Veterans' Administration, concerning National Service life insurance for syphilitics. A memorandum in reply was authorized containing two recommendations. Dr. Griffith's letter and the authorized reply appear herewith as Appendix A.

II. The Subcommittee next considered a letter from the Surgeon General U. S. Navy concerning acceptance by the Navy in enlisted or commissioned rank or the promotion to commissioned rank of persons with syphilis. The Subcommittee authorized a reply to the Surgeon General U. S. Navy. This correspondence is herewith appended as Appendix B.

III. The Subcommittee next considered certain tentative alterations in S.G.O. Circular Letter No. 74 dealing with the diagnosis and treatment of venereal disease. A number of changes, especially in the plan of procedure for the treatment of syphilis were tentatively agreed upon. It became clear, however, that a similar agreement concerning changes in the gonorrhea portion of this letter could not be reached during the meeting. It was therefore decided that a sub-group of the committee consisting of Drs. Cox, Herrold, Mahoney, and Nelson, would attempt revision of this portion of the letter for consideration at a subsequent meeting.

Following the meeting it was, however, agreed further by correspondence that the tentative recommendations as to syphilis should be withheld for the time being, pending further consideration. These tentative recommendations are therefore not included in these minutes.

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IV. At the request of the Surgeon General, U. S. Army, the Subcommittee considered the text of a tentative memorandum on biologic false positive serologic tests for syphilis. The Subcommittee agreed on the text of the tentative memorandum on this subject which is herewith appended as Appendix C.

V. At the request of the surgeon General U. S. Army, the Subcommittee next considered the text of a proposed circular letter on "The use of combined fever and chemotherapy in sulfonamide-resistant gonorrhea; and general considerations on the therapeutic use of physically induced fever." This memorandum had been prepared at a conference meeting held on April 6. Its text as prepared by that conference was approved by the Subcommittee. The Minutes of the Conference and the text of the approved memorandum are herewith included as Appendix D.

VI. At the request of a liaison officer from the Armed Services, the Subcommittee then considered the advisability of reducing the strength of protargol so much used in chemical prophylaxis. There have been numerous complaints concerning the irritating effect of the 2 per cent solution now in use. The Subcommittee approved the following recommendation:-

"NO INFORMATION EXISTS AS TO THE STRENGTH OF PROTARGOL SOLUTION EFFECTIVE IN THE PROPHYLAXIS OF GONORRHEA. HOWEVER, THERE IS AVAILABLE INFORMATION THAT IN THE TREATMENT OF ESTABLISHED GONOCOCCAL URETHRITIS IN THE MALE, ~~2~~ 0.5 PER CENT PROTARGOL SOLUTION APPEARS TO BE AS EFFECTIVE AS THE 2 PER CENT SOLUTION. THERE IS THEREFORE NO KNOWN CONTRAINDICATION TO REDUCTION OF THE STRENGTH OF PROTARGOL SOLUTION USED IN PROPHYLAXIS FROM 2 PER CENT TO 0.5 PER CENT."

VII. On March 17 the Committee on Drugs and Medical Supplies requested that the Subcommittee on Venereal Diseases explore the possibilities of substitutes for nepharsen and transmit their recommendations to the Committee on Drugs and Medical Supplies. This request eventuated in the approval by the Subcommittee of a letter to Dr. O. H. Perry Pepper, Chairman Committee on Medicine, together with an accompanying memorandum from Dr. Harry Eggle. This letter and the memorandum, if approved by the Committee on Medicine is to be forwarded to the Committee on Drugs and Medical Supplies. The letter and the memorandum are herewith enclosed as Appendix E.

VIII. The Subcommittee then considered certain recent information concerning oral prophylaxis with sulfathiazole. Colonel Turner reported on some experience at Army camps. The Chairman reported the result of certain recent studies of the effect of the sulfonamides on mental alertness and muscular coordination. There ensued a general discussion of the problem of sensitization to sulfonamides in relation to oral prophylaxis. The Subcommittee felt itself unable to make any recommendations on the subject of oral sulfonamide prophylaxis but agreed to reconsider the subject at its next meeting.

IX. The Subcommittee then considered the following proposals for OSRD contracts:-

a) Dr. Alexander A. Day. Improved methods of culture of the gonococcus. Proposal rejected.

b) Dr. Alan H. Chesney. The effect of vehicles on calonei in the prophylaxis of experimental syphilis. Proposal accepted and rated A.

c) Dr. Stafford L. Warren and Dr. H. C. Hodge. Absorption of arsenic through the intact and scratched skin of the rabbit as affected by vehicles and penetrants, etc. Held under advisement (see below).

d) Dr. Stafford L. Warren and Dr. L. T. Steadman. The effect of heavy metal inunctions on the prophylaxis of experimental syphilis in rabbits; the degree of absorption of mercury through the intact and scratched skin and subsequent distribution as affected by several variants.

These proposals by Drs. Warren and Hodge and Warren and Steadman seemed to the Subcommittee to be possibly affected by the recent departure of Dr. Warren from the University of Rochester. The Chairman was directed to write to Dr. G. H. Whipple, Dean University of Rochester Medical School, concerning the effect of Dr. Warren's absence on these proposals and on receipt of a reply from Dr. Whipple, to recircularize the members of the Subcommittee.

e) Dr. Charles M. Carpenter. The effect of fever on the distribution of arsenic in the tissues of rabbits injected with napharsen.

Members of the Subcommittee raised certain questions with regard to this proposal. The Chairman was directed to write to Dr. Carpenter for certain additional information, on receipt of which the proposal was to be recircularized.

f) Dr. Charles M. Carpenter and Dr. Stafford L. Warren. The effect of heavy metal inunctions on the prophylaxis of experimental syphilis in rabbits, the influence of the vehicle.

The members of the Subcommittee raised certain questions with regard to this proposal. The Chairman was directed to write to Dr. Carpenter for certain additional information, on receipt of which this proposal was to be recircularized.

X. The Chairman then reported to the Subcommittee on the results of several conferences held under the auspices of the Subcommittee since its last meeting. These were the conferences of December 29, 1942, and March 12, 1943, on human experimentation in gonorrhoea; and the conference of January 20 - 21, 1943, on the prophylaxis of venereal disease.

XI. The Subcommittee then approved a number of interim actions taken by the Chairman since the last meeting of December 1, 1942, having to do with nine OSRD proposals for original, supplementary, or extension of contracts.

At 7:30 P.M. the meeting adjourned.

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APPENDIX A

April 8, 1943.

Dr. Lewis H. Wood, Chairman,
Division of Medical Sciences
National Research Council
Washington, D.C.

Dear Doctor Wood:-

On March 13th you submitted to the Subcommittee on Venereal Diseases a copy of a letter from Dr. Charles H. Griffith, Medical Director, Veterans' Administration, dealing with the problem of syphilis in applicants for National Service life insurance. A copy of that letter is herewith appended.

Additional information not included in that letter is as follows:-

United States Government ("War Risk" of World War I) life insurance is no longer available except under certain restricted conditions, to veterans of that war. It has been replaced by National Service Life Insurance as of Oct. 8, 1940. The major difference between the two types of insurance is that old War Risk insurance provides waiver of premiums and compensation at \$5.75 per month per \$1,000. of insurance for total and permanent disability, while National Service Life Insurance provides waiver of premiums only.

The original act establishing National Service Life Insurance on Oct. 8, 1940, provides that any person entering active service in the Armed Forces is eligible for insurance without medical examination, if application is made within 120 days after entrance. If, however, he was in active service on October 8, 1940, he must apply within 120 days and must also furnish evidence satisfactory to the administrator that he is in good health at the time of the application.

The original act contemplated that if a person failed to apply for insurance within 120 days, he was ineligible to receive it at all; but as subsequently amended (December 1941) it was provided that he might apply after 120 days and at any time during active service, but must then furnish evidence that he is in good health.

The effect of these provisions has been to grant insurance without medical examination to all persons enrolled since October 8, 1940, if they applied for insurance within 120 days; but if application is delayed for more than 120 days, or if the person was in the Armed Forces before October 8, 1940, evidence of good health must be furnished. Likewise the same provisions as to evidence of good health apply to veterans of the last war who now apply for or seek to reinstate old War Risk Insurance.

It is stated that to March 31, 1943, 7,390,205 policies have been issued under National Service Life Insurance without medical examination (these including of course many persons with syphilis). From October 8, 1940, to March 31, 1943, 541,354 applications have been made by those in whom good health must be demonstrated.

Dr. Wood-2

Of these 7,512 have been rejected as not in good health; and of these rejections about 70 per cent (about 5200) have been rejected because of syphilis.

The words "good health" are not defined in the act of Congress establishing National Service Life Insurance, but are defined by the Veterans' Administration in the language quoted in Dr. Griffith's letter.

The Veterans' Administration has interpreted any evidence of syphilitic infection, past or present, whether obtained from history, physical examination, or laboratory tests, and regardless of previous treatment or the present condition of the patient, as evidence that an applicant for insurance is not in good health, and all applicants who have ever had syphilis and who, by virtue of the wording of the law, are required to demonstrate good health, are rejected.

The Veterans' Administration is unable to alter the provisions of application for insurance before the 120th day or the alternative demonstration of good health after that time. Likewise it is under the necessity of treating in identical fashion veterans of the last war who now apply for War Risk Insurance or reinstatement of lapsed policies under that insurance scheme, and members of the present Armed Forces eligible for National Service Life Insurance. These provisions are required by Congress. Furthermore, it is not possible under the terms of the law (a) to insure a syphilitic for the duration of the war only, since Congress has made no exceptions in providing that the five-year term insurance available for the duration may be converted into ordinary life insurance; (b) to permit a syphilitic or other person not in "good health" to waive his specific disability; or (c) to accept persons not in "good health", including syphilitics as substandard insurance risks with a write-up in premium rate.

Dr. Griffith's letter, after outlining the provisions under which syphilitics are accepted into the Armed Forces and after discussing the question of cure of syphilitic infection, asks the following question:- "Whether any rule based upon the passage of time or any other criteria may be used to determine when a person who has been infected with syphilis may be reasonably considered to be free from any further effects of the disease."

The Subcommittee on Venereal Diseases with the aid of representatives of the Veterans' Administration and certain actuaries and statisticians, would reply to the specific question posed by Dr. Griffith as follows, and asks that this reply be regarded as a recommendation to the Veterans' Administration:

PRESENT ACTUARIAL KNOWLEDGE DOES NOT PERMIT THE DEFINITION OF ANY RULING BASED UPON THE PASSAGE OF TIME WHICH MAY BE USED TO DETERMINE WHEN A PERSON WHO HAS BEEN INFECTED WITH SYPHILIS MAY BE REASONABLY CONSIDERED TO BE FREE FROM ANY FURTHER EFFECTS OF THE DISEASE. HOWEVER, IT IS POSSIBLE TO SAY THAT FOR ALL PRACTICAL PURPOSES A PERSON WHO HAS BEEN ADEQUATELY TREATED FOR EARLY OR FOR LATENT SYPHILIS, IS REASONABLY FREE

Dr. Weed- 3

FROM ANY FURTHER EFFECTS OF THE DISEASE, MAY BE PRESUMED TO BE IN "GOOD HEALTH" AS DEFINED BY THE VETERANS' ADMINISTRATION, AND SHOULD BE ELIGIBLE FOR GOVERNMENT OR NATIONAL SERVICE LIFE INSURANCE.

FOR THE PURPOSES OF THIS RECOMMENDATION, EARLY SYPHILIS IS DEFINED AS CLINICAL AND LABORATORY EVIDENCE OF PRIMARY OR SECONDARY SYPHILIS AT THE TIME OF START OF TREATMENT. LATENT SYPHILIS IS DEFINED AS SYPHILITIC INFECTION, CONGENITAL OR ACQUIRED, MANIFESTED ONLY BY A CONFIRMED POSITIVE SEROLOGIC TEST OF THE BLOOD AT THE START OF TREATMENT, THE CEREBROSPINAL FLUID HAVING BEEN DEMONSTRATED AT SOME TIME TO BE NORMAL.

ATTENTION IS DIRECTED TO THE FACT THAT IN THE ARMED FORCES THE OVERWHELMING MAJORITY OF SYPHILITICS APPLYING FOR NATIONAL SERVICE LIFE INSURANCE FALL INTO THE TWO CATEGORIES OF EARLY AND LATENT SYPHILIS AS DISTINGUISHED FROM OTHER FORMS OF LATE SYPHILIS, AND THAT ALL OF THEM HAVE BEEN, BEFORE ENTRY INTO THE ARMED SERVICES OR WILL BE AFTER SUCH ENTRY, ADEQUATELY TREATED FOR SYPHILIS.

A DEFINITION OF ADEQUATE TREATMENT FOR EARLY AND LATENT SYPHILIS WILL BE PREPARED, IF DESIRED, BY A SUBGROUP COMPOSED OF DOCTORS J.E. MOORE AND JOHN H. STOKES OF THE SUBCOMMITTEE ON VENEREAL DISEASES, LT. COL. T.B. TURNER (MC) U.S. ARMY, LT. COMDR. W.H. SCHWARTZ (HC) U.S. NAVY, AND A DESIGNATED REPRESENTATIVE OF THE VETERANS' ADMINISTRATION.

Furthermore, it appears to the Subcommittee on Venereal Diseases that there is urgently needed a reevaluation of the actuarial hazard imposed by various types of syphilitic infection under varying circumstances of treatment. It is felt that this information, if obtainable, would permit the adoption of a sound actuarial policy, not only by National Service Life Insurance, but also by commercial companies as well. To this end the Subcommittee recommends that:

A CONFERENCE SHOULD BE CALLED UNDER THE AUSPICES OF THE SUBCOMMITTEE ON VENEREAL DISEASES, NATIONAL RESEARCH COUNCIL, TO CONSIDER THE ACTUARIAL HAZARDS OF SYPHILIS. THE PERSONNEL OF THIS CONFERENCE, TO BE CHOSEN BY THE CHAIRMAN SUBCOMMITTEE ON VENEREAL DISEASES, SHOULD INCLUDE REPRESENTATIVES OF THE VETERANS' ADMINISTRATION AND OF COMMERCIAL LIFE INSURANCE COMPANIES, SYPHILOLOGISTS, AND INDEPENDENT STATISTICIANS. THE CONFERENCE SHOULD OFFER SUGGESTIONS FOR MODIFICATION OF CURRENT ACTUARIAL PRACTICE AS TO SYPHILIS ON THE BASIS OF EXISTING KNOWLEDGE: SHOULD OUTLINE WHAT FURTHER STUDIES MAY BE NEEDED, AND OFFER SUGGESTIONS AS TO WHEN, WHERE, BY WHOM, AND IN WHAT MANNER SUCH FURTHER STUDIES SHOULD BE PROSECUTED.

Sincerely yours,

S/ J. E. Moore, M.D., Chairman,
Subcommittee on Venereal Diseases.

VETERANS ADMINISTRATION

WASHINGTON

March 11, 1943

Dr. Lewis H. Reed
Chairman, Division of Medical Sciences
National Research Council
2101 Constitution Avenue
Washington, D. C.

~~CONFIDENTIAL~~

Dear Sir:

In conformance with telephonic conversation this date with Dr. Hugo Della, of my staff, there is submitted herewith a statement of a problem which has been giving concern to the Insurance Service of the Veterans' Administration, that is, applications for National Service Life Insurance from applicants who are members of the Armed Forces and who give a history of syphilis. The Director of that Service has asked the Medical and Hospital Service for an opinion and it will be appreciated if you will submit the problem to the appropriate committee of the Division of Medical Sciences of the National Research Council for their opinion on the question asked in the final paragraph of the quoted material.

"Statistics up to this time in connection with considered applications for National Service Life Insurance indicate that approximately 2% of the total applications received have been rejected for failure to meet medical requirements as established by the definition of good health, which is defined by the Veterans' Administration as: 'The words "good health" when used in connection with insurance, mean that the applicant is free from disease, injury, abnormality, infirmity, or residual of disease or injury to a degree that would tend to weaken or impair the normal functions of the mind or body or to shorten life.' Out of the total rejected cases it further appears that approximately 70% were rejected because of history of syphilis.

"Many protests have been received from applicants and military authorities with reference to these rejections, the familiar argument being cited that since the applicants are doing full military duty and have been found physically fit therefor, they are being unjustly deprived of protection intended to be afforded to them at the time of the enactment of the National Service Life Insurance Act. The protests are from various types of applicants, such as (a) those who contend and are able to prove that they received intensive luetic treatment some years ago and have no residual effects demonstrable at this time, (b) those who contend that diagnosis of syphilis has never been established and where the record shows there was no positive Wassermann reported but where intensive treatment following diagnosis by darkfield examination

apparently arrested the disease and no other clinical manifestations ever appeared and (c) those who contend that the luetic infection, if present, is of congenital origin.

"The War and Navy Departments are both accepting under the Selective Service Act inductees who have been treated and found cured of syphilis under the criteria of 'cure' as established by the United States Public Health Service in conjunction with the Surgeons General of the Army and Navy. The accepted persons are given general military and naval duty and many are now serving on foreign battlegrounds or the high seas.

"The policy of the War Department with reference to the acceptance for induction through the Selective Service System of registrants with a history of syphilis is as follows:

'Registrants with (1) confirmed positive serologic tests for syphilis and no clinical manifestations of the disease, or (2) with convincing histories of a trustworthy diagnosis of syphilis; or (3) of treatment for the disease on serologic or clinical grounds even though such evidence may possibly have been inadequate, may be considered for Class 1-A --

'(a) Provided that a negative spinal fluid since infection and treatment has been reported from a trustworthy source; and

'(b) Provided that in infections estimated to be of less than 4 years' duration, at least 30 to 40 arsenical and 40 to 60 insoluble bismuth injections or its equivalent, with a minimum total of 75 injections, have been given with approximate continuity (no rest periods or lapses) during the first 30 weeks of treatment; and

'(c) Provided that except as further qualified below, in infections estimated to be of over 4 years' duration, at least 20 arsenical injections and 40 to 60 insoluble bismuth injections or its equivalent, with a minimum total of 60 injections have been given in alternating courses; rest periods between consecutive courses not exceeding 8 weeks, being allowable.

'Evidence of duration of the infection shall be weighed by the examiner with due regard for age, general venereal history and medical guidance of the registrant.

'In infections of unknown duration it shall be presumed for classification purposes that those registrants under 26 years of age are of less than 4 years' duration, and over 26 years, of more than 4 years' duration.

'In congenital infections and in acquired infections of more than 10 years' known duration, in which no clinical progression occurred since treatment was begun; and in which a normal spinal fluid and negative physical examination is recorded not less than 2 years after treatment was terminated, the infection shall be regarded as "quiescent," and the registrant eligible for Class 1-A, provided the treatment in question shall have included 20 arsenical and 20 heavy metal injections.

'For the determination of treatment, the signed statements of acceptable treatment sources administering it with total number of doses of each drug and approximate calendar dates of administration and available laboratory and clinical data shall be required as evidence.'

"ARMY REGULATIONS: MEDICAL DEPARTMENT - PREVENTION OF COMMUNICABLE DISEASES

40-235

c. SYPHILITIC REGISTER -

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'A syphilitic register on W. D., M.D. Form No. 78 (Syphilitic Register) will be initiated and maintained for each person in active military service who has syphilis. The register will be opened by the medical officer who makes the diagnosis and will be continued until the subject is "cured" or is separated from the service. The term "cured" is used for administrative as well as medical purposes. The origin of the infection, initial diagnosis, and lesions will be noted under the proper headings, while other important manifestations and comments worthy of notation will be placed under "Progress of case." All serum reactions will be recorded, using the symbols specified on W.D., M.D. Form No. 55q (Clinical Record - Serological Reactions). All data relative to therapeutic measures taken will be noted in the register. All entries made in the register will be signed by the responsible officer. The register will be kept on file in the office of the surgeon of the station or command to which the patient is assigned and if the patient is transferred his register will be forwarded directly to the surgeon of his new station. The patient may be considered "cured" and the register closed when the patient has manifested no symptoms of syphilis for a period of one year during which he has received no treatment and has had two or more negative Wassermann reactions and no positive ones. Whenever possible, a negative spinal fluid examination should also be part of the standard of "cure." If the patient leaves the service before a "cure" has been accomplished, the register will be closed with appropriate remarks to that effect; also the necessity for uninterrupted completion of treatment will be carefully explained to the patient and he will be furnished with a written summary of the clinical features of his case and of the treatment

that he has received, so prepared as to enable other physicians to continue the treatment intelligently. A copy of this summary will be incorporated in the register. On "cure" or separation from the service the register will be forwarded to The Surgeon General.'

"MANUAL OF THE MEDICAL DEPARTMENT UNITED STATES NAVY No. 77

P-2350(b)

Section VIII. THE SYPHILITIC ABSTRACT

'Whenever a diagnosis of syphilis is made, it is the duty of the medical officer to carefully and fully explain to the patient the nature of the infection and that prolonged treatment is necessary to effect a cure. The patient shall then be instructed to sign the statement in the abstract; if he declines to do so, an entry to that effect shall be made. With regard to statements in rebuttal, medical officers shall be guided by instructions contained in paragraph 5, article 1196, Navy Regulations, 1920, and paragraph 2289 of this manual.'

'The policy of the Navy Department with reference to the acceptance of persons for enlistment giving a history of syphilis, is as follows:-

'Because of reasons peculiar to the Naval Service, applicants for original entrance who have syphilis in any stage, a definite history of, or who are persistently sero-positive, are not accepted. Discharged personnel with a history of syphilis contracted during previous service, who apply for reenlistment, are considered individually, taking into account date of infection, extent and continuity of treatment, time elapsed since treated, and results of physical examination, including that of the blood and spinal fluid. Such men accepted for reenlistment are considered physically qualified regardless of the previous history.'

'With respect to medical authorities and the indication that there is probably a change of viewpoint among such authorities as to the curability of syphilis, attention is invited to the following:

'J. E. Moore, M.D., Associate Professor of Medicine, Johns Hopkins University School of Medicine, in his recent book 'Modern Treatment of Syphilis' published in 1941, defined cure as follows:

- '1. That the patient becomes and remains symptomatically well for a lifetime.
- '2. That he is incapable of transmitting the infection to others.
- '3. That in addition he becomes and remains serologically negative

as to blood and spinal fluid.'

"He further classifies cure into three varieties: 1. Biologic, 2. Serologic, and 3. Symptomatic. By biologic is meant the eradication of the last remaining spirochete so that the patient is, with reference to his syphilitic infection, in the same state as before he acquired the disease. Serologic cure means that the patient's laboratory tests of blood and spinal fluid become and remain persistently negative. Symptomatic cure means that the patient becomes and remains well so far as syphilis is concerned for the duration of his lifetime. There may be, however, a persistence of the positive Wassermann.

'The pathology of syphilis has been studied by many observers, chief among whom is Warthin, who made the subject the major effort of his life's work. In a number of important contributions he has pointed out the great frequency of microscopic lesions which he attributes to syphilis, in patients in whom the disease was clinically quiescent or apparently "cured." In 1675 necropsies on patients over 25 years of age performed on his service between the years 1909-1923, he found what he calls lesions of latent syphilis in 501, or 29 per cent. To illustrate the inefficacy of modern treatment methods, he says that he has "never seen at necropsy a case of perfectly healed syphilis," though how anyone could recognize the presumably non-existent lesions of "perfectly healed syphilis" is not apparent. His various publications convey the impression that in his patients syphilis must often have been the cause of death, and tend, in our opinion, to over-emphasize its importance as a killing disease. Though the major burden of Warthin's argument was to illustrate the great prevalence of syphilis in the general population, rather than to emphasize its importance as a cause of death, it is unfortunate that he, the most assiduous student of the pathology of the disease, did not furnish details as to four important facts: (1) the cause of death, (2) whether the syphilitic infection was recognized during life, (3) the degree and extent of pathologic damage to serve as an index of functional incapacity, and (4) exactly what treatment had been given to those patients whom he classifies as clinically "cured" but pathologically still active.

'That the presence of microscopic lesions according with Warthin's criteria does not necessarily imply sufficient anatomic damage to produce physiologic or functional disability is indicated by the fact that another competent pathologist, Symmers, working at Bellevue Hospital, could find gross (not microscopic) lesions of syphilis in only 6.5 per cent of 4,880 autopsies. Not even in all of these patients were the lesions of syphilis, visible to the naked eye, responsible for the patient's death!

"Dr. David P. Barr, Busch Professor of Medicine, Washington University

School of Medicine, in 'Modern Medical Therapy,' published in 1940, gives the following table showing the percentage of cure of early syphilis.

<u>'Stage of Syphilis</u>	<u>Chance for Cure</u>
Seronegative primary syphilis	100%
Seropositive primary syphilis	95%
Early secondary syphilis	90 - 95%

"H. N. Cole, M.D., Professor of Clinical Dermatology and Syphilology, Western Reserve, in the September 1941 edition of the Journal of the American Medical Association, in an article on syphilotherapy, says the following about cure:

'The question now arises What group of syphilitic patients achieved the best results? The best outcome, 82 per cent of cures, was found in the group in which the diagnosis had been made early — in the seronegative primary phase of the disease. The poorest outcome was found in the group in which treatment was not started until the seropositive primary phase, as only 55% of these patients were cured. Cures occurred in 69% of patients with secondary syphilis when the patient had been able to build up some of his own immune powers and in 59% of patients with latent syphilis. Neurosyphilis was two and one-half times as frequent among those patients on whom treatment was begun in the seropositive primary phase of the disease. As in other stages of syphilis, relapse played an important role here, for there were three times as many cures among those patients who did not have a relapse as among those who did. Moreover, neurosyphilis was encountered six times as often in the latter group. Relapses should be prevented in patients with early syphilis if possible.

'What was the result as to system of treatment employed? Cures occurred in 83% when continuous treatment, as contrasted to intermittent or irregular treatment, was employed in the first six months of the disease, and this was raised to 90% if later treatment was also continuous. On the other hand, with irregular or intermittent treatment in the first six months, cures occurred in but 54%, and this was not altered if the same plan was continued. Yet if the irregular treatment was changed to continuous in the second six months, cures rose from 53% to 73%, while cures in the group given continuous treatment the first six months fell from 83% to 75% with irregular treatment the last six months'.

"It should be here interpolated that continuous treatment means giving of the prescribed drugs at least once a week for a period of at least a year, with no intervening rest periods.

"Paul Padget, M.D., Associate Professor of Medicine, Johns Hopkins School of Medicine, in an article in the Journal of the American Medical Association, January 4, 1941, entitled, 'The Treatment of Early Syphilis', reviewed and analysed the material from the Johns Hopkins Hospital Clinic and found 551 patients who had been completely reexamined five years after termination of original treatment and of these, 273 had been followed for ten years or more. Of these 273, 179 had been observed at approximately five years after termination of original treatment and were classified as cured at that time. Those 179 when they were reexamined at the ten year period, continued to be classified as cured. In commenting upon this study Dr. Joseph E. Moore stated:

"This is the first large scale long term evaluation of treatment results in early syphilis available. From it may be singled out three points for special comment: 1. Padget's data justify the opinion that in early syphilis five year "cure" represents permanent "cure." Patients who were clinically and serologically normal five years after treatment ended were still normal after five or more further years of observation. From the purely scientific point of view, the data are as yet inadequate to permit this statement to be too dogmatically made; and the necessity of further long continued observation of these and similar patients still continues, in order particularly to rule out the later development of cardiovascular syphilis, the average incubation period of which is twenty to twenty five years after infection. From the more purely practical individual and public health point of view, however, the apparent fact of the permanence of five year "cure" is of great importance, since it does permit some relaxation of post-treatment follow-up, after the fifth year of observation, in general medical and clinic practice.

"2. The curability of early syphilis is favorably influenced by the amount of arsenical treatment given in the early months, preferably the first three months. The more trivalent arsenical given in this time period the better the chance of ultimate "cure." This fact has perhaps an important bearing on the new "five-day treatment" of early syphilis by massive dose and continuous intravenous drip. Nevertheless it is to be observed from Padget's data that patients who receive so little treatment as only four to six injections of an arsphenamine by conventional divided dose technique have a 60% chance of five year "cure" with practically no risk of hemorrhagic encephalitis or death. The incidence of the serious reaction of hemorrhagic encephalitis with conventional methods of treatment is probably somewhere between one in 15,000 and one in 25,000 patients treated. With the new "five-day treatment," the chance of "cure" probably lies somewhere between 70 and 85 per cent, depending on whether metharsen or neoarsphenamine is used; i.e., a chance of "cure" only 10 to 25 per cent greater than from only four to six conventional doses of an arsphenamine, and no greater than

with the best available continuous outline of treatment applied for twelve to fifteen months; but with a risk of the development of hemorrhagic encephalitis of approximately two hundred fold greater than with conventional methods.

13. Even with a few injections of an arsphenamine only, patients may be maintained indefinitely in a state of health, so far as syphilis is concerned, in the proportion of about 80 per cent. With the best available conventional methods of treatment, 90 per cent of patients achieve long-term "cure" by both clinical and serologic standards, and the amazingly high total of 95 per cent are clinically "cured."

"Information received also indicates that at the present time many private insurance companies will approve applications for those showing a cured condition and as stated in the 'Rules for Lay Underwriters' by the Prudential Life Insurance Company, 'Cured or apparently cured cases are the only ones that are acceptable.'

"In view of the above, it is requested that the matter be further considered by the Medical Director in the light of existing medical knowledge and information furnished as to whether any rule based upon the passage of time or any other criteria may be used to determine when a person who has been infected with syphilis may be reasonably considered to be free from any further effects of the disease."

It will be greatly appreciated if you will submit the report of the Division of Medical Sciences to my office.

Very truly yours,

(Signed) Charles H. Griffith

Medical Director

APPENDIX B

Washington, D.C.

March 23, 1943.

Dear Dr. Weed:-

The significance of a history of a clearly defined infection with syphilis, as it affects the fitness of enlisted men of the Navy for advancement to commissioned or warrant rank and as it affects the fitness of applicants for enlistment or appointment to commissioned or warrant rank from civilian life, is being reappraised.

Under present instructions, a candidate for appointment to warrant or commissioned rank from among the enlisted men of the Navy, in whose case there is a history of a clearly defined infection with syphilis, must have negative serological examinations of his blood and cerebrospinal fluid at the time of the physical examination to determine his fitness for appointment. In addition, any clinical or serological evidence of active or latent syphilis which may be recorded during the preceding five years, or of central nervous system involvement at any time, is disqualifying for appointment.

Applicants for enlistment are not accepted if serological tests are positive for syphilis and applicants for appointment to officer status from civilian life are not accepted if serological tests are positive for syphilis, or if there is a history of a clearly defined infection with syphilis. Applicants for appointment to officer status from civilian life, however, who have had previous Naval service and in whose cases there is a history of syphilis, but whose current serological reaction is negative, are required to present evidence showing that there has been no active or latent syphilis during the preceding five years, that treatment has been adequate, and that there is no past or present evidence of involvement of the central nervous system.

The question has been raised whether under modern methods of treatment the requirement of a period of five years without evidence of activity in cases which have been properly treated is sound in the light of present knowledge of this disease and its treatment. The validity of the requirement that evidence of a central nervous system involvement at any time be disqualifying has also been questioned, particularly as applied to cases in which the evidence of central nervous system involvement consisted of positive findings in the spinal fluid, without clinical signs or symptoms and in which adequate treatment has been administered, followed by several years of negative findings in the spinal fluid.

It is requested that these problems be referred to the proper committee for investigation and report and for any recommendations which may be appropriate.

Sincerely,

Lewis H. Weed, M.D., Chairman
Division of Medical Sciences
National Research Council
Washington, D.C.

S/ Ross T. McIntire
Rear Admiral, (MC)
Surgeon General, U. S. Navy.

APPENDIX B

Baltimore, Maryland
April 9, 1943.

Dr. Lewis H. Weed, Chairman,
Division of Medical Sciences
National Research Council,
Washington, D.C.

Dear Doctor Weed:

On April 7, 1943, the Subcommittee on Venereal Diseases, National Research Council, has considered the letter of March 23, 1943, from the Surgeon General, U. S. Navy (copy herewith appended), asking certain questions as to the acceptance of applicants for enlistment or for commissioned or warrant rank from civilian life; and as to candidates for promotion to commissioned or warrant rank from among enlisted personnel, as these questions are affected by syphilis. The Subcommittee on Venereal Diseases offers the following recommendations and suggestions:

- (1) Enlisted personnel and warrant or commissioned officers who have or develop syphilis, should be governed by an identical policy, except as hereafter specified.
- (2) Applicants from civilian life for enlistment or for commissioned or warrant rank should be rejected if they show evidence of cardiovascular, visceral, or neurosyphilis (including asymptomatic neurosyphilis, except as suggested in paragraph 6-a below). This rejection is already automatic in the case of enlisted personnel made available to the Navy through Selective Service, and is governed by Selective Service "List of Defects", Jan. 16, 1943. For applicants for commissioned or warrant rank from other sources than Selective Service an identical policy should prevail.
- (3) Other syphilitic applicants for enlistment through Selective Service should be accepted, regardless of previous treatment or serologic status.

The disposition of such persons after enrollment should in general conform to the policy of the U.S. Army, which provides facilities at training centers for evaluation of previous treatment and for further treatment where necessary.

Candidates from civilian life for commissioned or warrant rank should be accepted regardless of the blood serologic status if there is no evidence of cardiovascular, visceral, or neurosyphilis, and if treatment for syphilis deemed to be adequate has been completed before the date of commissioning.

- (4) The requirement of a probationary period of five years, during which all serologic tests are negative, is unsound in the light of modern practice and should be abandoned. The persistent positivity or negativity of blood serologic tests after treatment have no apparent relation to the probability of subsequent progression or relapse, except in a small number of cases of early syphilis. The adequacy of treat-

Dr. Reed- 2

ment in other types of syphilitic infection must be arbitrarily defined, not on the basis of serologic outcome, but instead on the basis of percentage probability of clinical freedom from progression or relapse in large numbers of syphilitic persons subjected to varying amounts and types of treatment, and thereafter followed for long periods of time. Viewed in this manner any syphilitic person who has completed the amount and kind of treatment adjudged necessary for the stage of disease existent at the start of treatment (e.g., early syphilis, latent syphilis), may be regarded as "probably cured" on the completion of that amount of treatment; and treatment may be discontinued regardless of the blood serologic response, but not without a negative spinal fluid examination.

(5) The existence of a history of syphilis should not constitute an impediment to promotion, unless for reasons of actual physical disability. Promotion to or in commissioned or warrant rank, or the acceptance of persons from civilian life in such rank, should rest upon all of the following: (a) proof of completion of "adequate" treatment* for latent syphilis or its current administration; (b) the demonstration of a normal spinal fluid at some time after completion of that treatment in the case of early syphilis, or before, during, or after treatment in the case of latent syphilis; (c) freedom from clinical evidence of cardiovascular, visceral, or neurosyphilis; and (d) regardless of the positivity or negativity of the blood test. In persons whose treatment was begun for early syphilis, there should be required, in addition, 6 months of persistent seronegativity of the blood.

(6) The question of neurosyphilis, asymptomatic or clinical, may properly be divided into two parts:- (a) the acceptance of such persons from civilian life in enlisted or commissioned rank; and (b) the disposition of such persons discovered to have neurosyphilis after entry into the Service.

(a) By and large, it is a sound rule that applicants from civilian life, who have or have had neurosyphilis, asymptomatic or clinical, should be rejected as imposing a special risk of eventual breakdown. This is certainly true administratively of applicants for enlistment. It would be desirable, however, if such persons, particularly those with asymptomatic neurosyphilis, could in certain exceptional instances be judged on their individual merits by a specially trained officer of the Venereal Disease Section, Division of Preventive Medicine.

(b) In the case of enlisted men or commissioned or warrant officers already in the Service, general paresis, advanced tabes dorsalis, and some cases of diffuse meningovascular neurosyphilis (especially those with predominantly vascular manifestations) should be cause for immediate medical survey or retirement, regardless of the type of duty performed. In other types of neurosyphilis (especially early tabes, most cases of diffuse meningovascular neurosyphilis, acute syphilitic meningitis, and all cases of asymptomatic neurosyphilis), a decision as

* A description of "adequate" treatment for early and latent syphilis will be furnished if desired.

Dr. Hood- 3

to whether the patient should be retained in or separated from the Service should depend on the type of duty involved, the availability of adequate treatment, and the patient's response to that treatment. In general, persons in this category are capable of shore duty in non-combat zones, thus releasing other personnel for combat.

(7) Aviation personnel, who are discovered to have syphilis or who acquire it after entry into the Service, constitute a special case. Present naval custom is that such personnel are permanently grounded. In view of the urgent need for such skilled persons, and of the adequacy of modern treatment methods for syphilis, it is suggested that this policy be reviewed.

It is believed that for early and latent syphilis the six-month treatment scheme adopted by the Army (S.G.O. Circular Letters Nos. 74 and 105) will be as productive of ultimately satisfactory results as the more prolonged methods of treatment heretofore in use in the Navy and elsewhere. For aviation personnel with early and latent syphilis, this treatment scheme could be condensed into a period of 10 - 12 weeks without material reduction in satisfactory results or greatly increased risk from treatment. It is suggested that in such personnel a shortened treatment scheme of this nature be adopted, the patient being grounded only during the actual period of treatment, and restored to flying status immediately on its completion.

(8) Intensive treatment for early syphilis also seems applicable to submarine or PT boat personnel, who should be regarded as fit for duty on its completion.

(9) Much of the objection of the Armed Forces to the acceptance of syphilis has heretofore rested on the necessity for prolonged (12-18 months) treatment. The adoption by the Army of a 6-month plan has removed this objection in that Service. It is believed that recent developments permit of even further condensation of treatment for early and latent syphilis; and it is suggested that the Navy adopt these modifications.

Very truly yours,

S/ J. E. Moore, Chairman,
Subcommittee on Venereal Diseases.

SUGGESTED TEXT OF A MEMORANDUM ON

BIOLOGIC FALSE POSITIVE SEROLOGIC TESTS FOR SYPHILIS

False positive serologic tests for syphilis may be divided into two categories; technical false positive reactions and biologic false positive reactions.

I. TECHNICAL FALSE POSITIVE REACTIONS

A. Physician or Nurse:

1. Bacterial contamination and hemolysis:
 - (a) non-sterile and wet syringes and test tubes
 - (b) improper storing of specimens
 - (c) delay in sending specimens to laboratory
2. Mislabeling of specimens
3. Accidental or intentional sending of oxalated or citrated specimens to the serodiagnostic laboratory.

B. Laboratory:

1. Dirty or improperly cleansed glassware
2. Inexact measurements of the materials used in the test
3. Faulty preparation or deterioration of the test materials
4. Improper preparation of the serums
5. Tests inadequately controlled or improperly read
6. Mistakes in recording, copying, and reporting the results of the tests.

The frequency of occurrence of these technical false positive reactions is usually proportional to the care exercised in the performance of tests and the skill and experience of the individual performing them.

II. SYPHILOID DISEASES.

Three diseases caused by spirochetes other than T. pallidum, namely, yaws, bejel, and pinta, will cause positive serologic tests for syphilis. Yaws is endemic in all tropical countries. Bejel occurs particularly in Syria; and pinta in the West Indies, Mexico, and Central and South America. These diseases, which are quite similar bacteriologically, serologically, and in their response to anti syphilitic treatment, may be designated as syphiloid or syphilis-like conditions. The positive serologic tests resulting from these conditions should not be considered as biologic false positive reactions, but as confirmatory of the diagnosis of the diseases in question.

III. BIOLOGIC FALSE POSITIVE REACTIONS IN INFECTIOUS DISEASES OTHER THAN SYPHILIS OR SYPHILOID DISEASES.

A. The most frequent of the diseases causing biologic false positive serologic tests and the approximate incidence of such tests in these various conditions is as follows:-

1. Vaccination against small-pox. Ten to thirty-five per cent of persons with vaccinia or vaccinoid reactions show false positive serologic tests these usually appearing about 12 days after vaccination, and persisting from several weeks to several months.

2. Malaria. The majority of malarial patients develop false positive serodiagnostic tests at some stage of the acute infection. In many instances the false positive tests persist for only a few days, but may persist for many months. The effect of long standing chronic malaria in producing persistent false positive tests is not yet evaluated.

3. Pneumonia and upper respiratory infections. Due to microorganisms or a virus, but particularly the latter, and other mild or severe upper respiratory infections, may produce false positive reactions in 5 to 20 per cent of affected persons, these persisting for a few weeks to many months.

4. Leprosy. False positive reactions occur in from 60 to 70 per cent of affected persons and persist indefinitely.

5. Infectious mononucleosis. Transitory false positive reactions lasting from a few days to several months, occur in about 20 per cent of affected persons.

6. Other conditions in which false positive reactions may occasionally occur are typhus, Weil's disease, recurrent fever, rat-bite fever, chancroid, lymphogranuloma inguinale, mumps, and perhaps other acute infections.

B. The false positive reactions occurring in acute infections other than syphilis or syphiloid diseases are usually weakly positive with a low serum reagin titre in quantitative tests. In general, and except in the case of leprosy, they tend to disappear spontaneously within 2 to 3 months after subsidence of the acute infection.

IV. SUGGESTED METHOD OF EVALUATION OF SUSPECTED BIOLOGIC FALSE POSITIVE SEROLOGIC TESTS FOR SYPHILIS

Evaluation of the occurrence of biologic false positive tests for syphilis in non-syphilitic conditions, especially some which are likely to complicate diagnosis in military service, particularly in sub-tropical regions, requires the following revision of procedure:

A. A single positive serologic test for syphilis or even several positive tests on the same specimen in the absence of convincing history or clinical evidence of syphilis, should not be made the basis of a diagnosis.

B. Repeated positive tests on successive specimens, strong or weak, should not, without further evidence, be made the basis of a diagnosis of syphilis if - -

- (1) The person is febrile at the time of (or just before) testing.
- (2) Vaccination for small-pox has taken place within the 3 preceding months, especially with "take."
- (3) There is evidence of active or recent malaria, febrile respiratory tract infection, influenza, infectious mononucleosis, mumps, typhus, leprosy, or other diseases listed above.

C. When such reasons for doubting the specificity of serologic test findings appear, antisyphilitic treatment should be withheld with repetition of the test every two weeks for 3 months. If the results remain positive or conflictingly positive and negative, the procedure described in (D) should, if possible, be carried through at an evaluation center under expert direction.

D. An examination to evaluate doubtful or conflicting serologic tests should include:-

- (1) An examination for stigmas of congenital syphilis, including such x-ray examinations as may be required, inspection of the ocular fundi, and slit-lamp examination of the corneae.
- (2) Additional serologic tests for syphilis utilizing several laboratory procedures.
- (3) Serologic tests or credible information thereon regarding parents, siblings, marital or sexual partners, and children as obtainable.
- (4) Serially repeated reagin unit titer determination on positive bloods by an accepted quantitative procedure, performed by a designated laboratory of the Army Medical Service.
- (5) Examination of the blood for plasmodia.
- (6) Differential blood count (infectious mononucleosis).
- (7) A heterophile antibody test.
- (8) If the patient is febrile, repeated blood cultures, x-ray of chest, other appropriate evaluative procedures.
- (9) An examination of the spinal fluid.
- (10) The so-called "provocative" injection of an arsenical drug is useless and should not be employed.

E. If in the opinion of a competent referee the results of such an examination are inconclusive, the individual is to be returned to duty without treatment for syphilis, and the serologic and laboratory studies repeated, if possible, excluding the spinal fluid examination, in 6 months; the entire laboratory study after 1 year, if necessary.

F. If no diagnosis of syphilis is arrived at, the discharge memorandum of such persons is to contain no reference to a diagnosis of syphilis and no syphilis register will be maintained. The case may, however, be cross-indexed to a reference file as biologically questionable serologic test results.

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6. Other conditions in which false positive reactions may occasionally occur are typhus, Weil's disease, recurrent fever, rat-bite fever, chancroid, lymphogranuloma inguinale, mumps, and perhaps other acute infections.

B. The false positive reactions occurring in acute infections other than syphilis or syphiloid diseases are usually weakly positive with a low serum reagin titre in quantitative tests. In general, and except in the case of leprosy, they tend to disappear spontaneously within 2 to 3 months after subsidence of the acute infection.

IV. SUGGESTED METHOD OF EVALUATION OF SUSPECTED BIOLOGIC FALSE POSITIVE SEROLOGIC TESTS FOR SYPHILIS

Evaluation of the occurrence of biologic false positive tests for syphilis in non-syphilitic conditions, especially some which are likely to complicate diagnosis in military service, particularly in sub-tropical regions, requires the following revision of procedure:

A. A single positive serologic test for syphilis or even several positive tests on the same specimen in the absence of convincing history or clinical evidence of syphilis, should not be made the basis of a diagnosis.

B. Repeated positive tests on successive specimens, strong or weak, should not, without further evidence, be made the basis of a diagnosis of syphilis if - -

- (1) The person is febrile at the time of (or just before) testing.
- (2) Vaccination for small-pox has taken place within the 3 preceding months, especially with "take."
- (3) There is evidence of active or recent malaria, febrile respiratory tract infection, influenza, infectious mononucleosis, mumps, typhus, leprosy, or other diseases listed above.

C. When such reasons for doubting the specificity of serologic test findings appear, antisyphilitic treatment should be withheld with repetition of the test every two weeks for 3 months. If the results remain positive or conflictingly positive and negative, the procedure described in (D) should, if possible, be carried through at an evaluation center under expert direction.

D. An examination to evaluate doubtful or conflicting serologic tests should include:-

(1) An examination for stigmas of congenital syphilis, including such x-ray examinations as may be required, inspection of the ocular fundi, and slit-lamp examination of the corneae.

(2) Additional serologic tests for syphilis utilizing several laboratory procedures.

(3) Serologic tests or credible information thereon regarding parents, siblings, marital or sexual partners, and children as obtainable.

(4) Serially repeated reagin unit titer determination on positive bloods by an accepted quantitative procedure, performed by a designated laboratory of the Army Medical Service.

(5) Examination of the blood for plasmodia.

(6) Differential blood count (infectious mononucleosis).

(7) A heterophile antibody test.

(8) If the patient is febrile, repeated blood cultures, x-ray of chest, other appropriate evaluative procedures.

(9) An examination of the spinal fluid.

(10) The so-called "provocative" injection of an arsenical drug is useless and should not be employed.

E. If in the opinion of a competent referee the results of such an examination are inconclusive, the individual is to be returned to duty without treatment for syphilis, and the serologic and laboratory studies repeated, if possible, excluding the spinal fluid examination, in 6 months; the entire laboratory study after 1 year, if necessary.

F. If no diagnosis of syphilis is arrived at, the discharge memorandum of such persons is to contain no reference to a diagnosis of syphilis and no syphilis register will be maintained. The case may, however, be cross-indexed to a reference file as biologically questionable serologic test results.

APPENDIX D

MINUTES OF A CONFERENCE ON THE USE OF COMBINED FEVER AND
CHEMOTHERAPY IN SULFONAMIDE-RESISTANT GONORRHEA

April 6, 1943.

At the request of the Surgeon General, U. S. Army, a conference was held in Washington, D.C. on April 6, 1943, under the auspices of the Subcommittee on Venereal Diseases, National Research Council on the use of combined fever and chemotherapy in sulfonamide-resistant gonorrhoea. The aim of the conference was to prepare a draft of Circular Letter to be sent out by the Surgeon General's Office to appropriate military hospitals.

The conferees included the following:

From the U.S. Army, Brigadier General C. C. Hillman, Brigadier General Hugh Morgan, Colonel Alden Freer, Lt. Colonel Malcolm J. Farrell, Lt. Colonel Thomas B. Turner, Lt. Colonel H. J. Shull, Major T. H. Sternberg, Lt. J. F. Shronts. From the Subcommittee on Venereal Diseases, Doctors J. E. Moore, J. F. Mahoney, and Oscar F. Cox. From the Mayo Clinic, Dr. Frank H. Krusen. From the University of Rochester, Dr. Charles H. Carpenter, and from the National Research Council Dr. G. M. Guest and Dr. T. H. Forbes.

This conference prepared a memorandum for submission to the Subcommittee on Venereal Diseases which is herewith appended.

The conference then adjourned.

Appendix D

SUBJECT: THE USE OF COMBINED FEVER AND CHEMOTHERAPY IN SULFONAMIDE-RESISTANT GONORRHEA; AND GENERAL CONSIDERATIONS ON THE THERAPEUTIC USE OF PHYSICALLY INDUCED FEVER.

I. INTRODUCTION:

The general indications for fever therapy in sulfonamide-resistant cases of gonococcal infections have been given in S. G. O. Circular Letters No. 74, July 25, 1942, and No. 86 August 18, 1942. While the effectiveness of artificial fever combined with chemotherapy in the treatment of this type of case has been well established, the difficulties and dangers inherent in the method are often underestimated.

This Circular Letter is published with a view to outlining in detail the basic principles of physically induced fever in order that serious reactions may be held to a minimum.

II. PERSONNEL:

a. The administration of fever therapy should be under the immediate and constant supervision of an officer of the Medical Corps who has had special training or experience in this field. Officers should be selected for this duty on a volunteer basis, rather than by designation merely because of experience in dermatology, urology, or other specialty; such medical specialization in itself, is usually of limited value as applied to physically induced fever therapy.

b. The actual administration of fever treatments will be by members of the Army Nurse Corps who have had special training for or experience with this method. As with medical officers, it is suggested that nurses be selected as technicians on a volunteer basis. Only those nurses with a genuine interest in this field are likely to give satisfactory performance over a long period of time.

c. When any patient is actually under treatment with fever therapy, the medical officer experienced in fever therapy should be constantly in attendance or immediately available for prompt call.

d. "Special training or experience" in fever therapy as applied to Medical Officers and Army nurses should represent a minimum of 6 weeks of training in a special center or its equivalent in terms of actual previous experience.

III. EQUIPMENT:

a. The employment of any type of diathermy machine for the purpose of inducing fever, either alone or in conjunction with a cabinet, is not recommended.

The type of fever cabinet is of no material importance so long as it is well constructed. However, certain items of equipment are considered to be necessary adjuncts to the administration of treatment. These include: an electrical rectal indicating thermometer (where this equipment is not available or is temporarily out of order, certified clinical rectal thermometers may be used, though this procedure is not recommended); oxygen tanks complete with reducing

valve, flow-meter, and humidifying device; rubber nasal catheters of the latex type, and oro-nasal face masks of the BLB type or face tents; electric fans; equipment for the intravenous infusion* of both bulk and concentrated dextrose solutions; hypodermic outfits; a bed for the patient to rest in following treatment; and the necessary amounts of linen, towels, washcloths, etc.

b. Standardization of electric thermometer. The electric thermometers must occasionally be checked for accuracy of temperature recordings. This is best accomplished by use of a constant temperature mercury pot. If such equipment is not available, a simple method which ensures acceptable accuracy is as follows: An ordinary thermos bottle is filled approximately three-quarters full of water at a temperature of slightly more than 106°F. In the water are placed three large "laboratory type" certified mercury thermometers, the degree calibrations of which are spread over a sufficient range to permit easy reading, and the rectal bulb of the thermometer cable. With the water in constant motion, the readings of the three mercury thermometers and the electric thermometer should be recorded simultaneously. The average reading of the mercury thermometers should be compared with that of the electric thermometer. If no more than 0.2°F. difference between the two is noted, no change in standardization of the electric thermometer should be attempted. If there is consistent variation of more than 0.2°F., the change in standardization of the electric thermometer should be made in accordance with the recommendations of the manufacturer. It is important that standardization be checked only at a temperature of 106°F.

c. The rooms in which fever therapy is given should present a cheerful appearance. They should be well lighted and well ventilated and should be large enough to prevent any impression of crowding of equipment.

IV. SELECTION OF PATIENTS FOR FEVER THERAPY:

a. In general, patients with gonorrhoea selected for physical fever therapy will be those who have proved to be sulfonamide-resistant after adequate trial of chemotherapy and such other adjuvant measures as are prescribed in Circular Letter No. _____.

b. Of primary importance is the establishing of an accurate diagnosis. With respect to those patients considered to have gonorrhoea, it is suggested that when possible the diagnosis be confirmed by cultural means. Those cases of urethritis with questionable or even "positive" smear findings and consistently negative cultures for N. gonorrhoeae are apt to respond indifferently to treatment by fever-chemotherapy.

c. Candidates for fever therapy should meet the following standards:

- (1) Negative cardiovascular examination, including normal EKG.
- (2) Negative chest X-ray at this hospital admission.
- (3) Essentially normal blood picture (white and red cell counts and hemoglobin).

* If new rubber (not latex) tubing is used for intravenous infusions, it should be soaked in 4% sodium hydroxide solution for several hours and then thoroughly rinsed before use. This is to avoid a febrile "tubing" reaction.

(4) Normal kidney function as measured by routine urine examination and dilution-concentration (fisberg) test.

(5) Normal serum bilirubin or other liver function test in those cases giving a history of jaundice due to hepatitis or other causes.

(6) Of these examinations, the cardiovascular is the most important. In addition, if the history or careful physical examination reveals other abnormalities, these factors must be carefully evaluated before subjecting the patient to fever-chemotherapy.

d. Finally, each patient to be considered for fever therapy should be interviewed by the officer in charge of fever therapy for two reasons: (1) to establish rapport with the patient so that he will not feel that someone entirely strange to him is to supervise his fever treatment (which for the majority of individuals is a new experience); and (2), to enable the officer to estimate the psychic stability of the candidate. Physically induced fever cannot be administered to a non-cooperative patient. The whole-hearted cooperation of the vast majority of patients can be gained by the simple expedient of frankly discussing the general features of the treatment and informing him what is to be expected of him. Those individuals who are fearful, reluctant to accept the necessity for the treatment, and who appear to be emotionally unstable are poor candidates for fever and usually, if placed in the cabinet, discontinue the treatment themselves. At the discretion of the medical officer, fever therapy for this type of patient may be deferred indefinitely.

V. PREPARATION OF THE PATIENT FOR FEVER THERAPY:

a. Fluids and salt. A tablespoonful of common table salt is dissolved in a glass of water and sipped at intervals during the course of the afternoon and evening preceding the fever treatment. This intake is to be prolonged over approximately an 8-hour period. Other fluids are permitted ad lib.

b. Diet. The regular hospital diet is administered the day preceding treatment. No food should be given the morning of treatment, except that coffee and dry toast up to half an hour prior to treatment may be permitted if the patient desires.

c. Enema. A mild soapsuds enema is administered about 9:00 P.M. the evening preceding treatment. If adequate evacuation is not obtained, the enema should be repeated the same evening.

d. Chemotherapy. A minimum lapse of one week should intervene between the last previous chemotherapy and the administration of combined fever-chemotherapy. Immediately preceding fever treatment the following dosage scheme is suggested for those patients with gonorrhea: Sulfathiazole is the drug of choice. Treatment is started on the day preceding fever therapy; two grams of this drug are given at 12:00 noon, 4:00 P.M. and 8:00 P.M.; 1 gram at 12:00 midnight, 4:00 A.M., and 6:30 A.M. The fever treatment should be begun as early in the morning as is feasible.

e. Patients who have previously suffered from serious sulfonamide reactions should be treated with fever only.

f. Sedation. To insure sufficient rest the night preceding treatment, it is of advantage to administer a mild sedative at bedtime. It is suggested that such sedative be either phenobarbital 0.1 gm. or nembutal 0.1 gm.

VI. CARE OF THE PATIENT DURING FEVER THERAPY:

a. Amount of fever. On the basis of recent experience it is recommended that patients be given 8 hours of fever at 105.8 - 106.2 degrees F. The latter temperature (106.2F) should not be exceeded. With the administration of the amount of pre-fever chemotherapy noted above, the incidence of vascular instability is greater in the zone above 106.2 as compared with that noted at recommended temperature levels. Periods of treatment shorter than 8 hours appear to be less effective.

b. Oxygen. This is administered continuously throughout the treatment, including the induction phase. The simplest means of supplying oxygen to the patient is the nasal catheter. The oxygen so administered must be adequately humidified prior to inhalation. A flow rate of 6 liters per minute is recommended.

c. Fluids. Bulk intravenous fluids should preferably be given only in the presence of hemoconcentration as demonstrated by falling systolic blood pressure below 90 m.m. mercury or by increased hemoglobin or blood specific gravity. In practice, however, patients who cannot tolerate fluids by mouth in adequate amounts must have fluids administered intravenously, or have the treatment discontinued.

(1) Oral. An average of 500 cc. of fluids per hour appears adequate for most patients. Many patients are not so thirsty toward the latter part of the treatment and fluids should not be forced under these circumstances. The larger part of the fluid intake, therefore, should be administered during the forepart of the treatment. The fluids should be given iced and approximately half the hourly intake should be in the form of 0.3 - 0.6 per cent saline solution; the remaining intake may be in the form of plain water or one of the solutions described below under "d."

(2) Intravenous.

(a) The infusion recommended is 10 per cent dextrose in normal saline; the total amount should be administered slowly and should not exceed 2000 cc. Hypertonic solutions should be given. Isotonic solutions are less effective. Hypotonic solutions are contraindicated.

(b) Concentrated intravenous fluids in the form of 50 per cent dextrose are administered in an effort to correct minor degrees of vascular instability. This procedure is most effective when administered early, shortly after the appearance of signs of beginning vasomotor decompensation. Too much emphasis cannot be placed on the prompt recognition of these early signs (see

Section IX). To delay corrective measures until the appearance of clinical shock increases the risk of continuation of treatment enormously; the institution of corrective measures early almost always assures the successful completion of treatment. The 50 per cent dextrose should be administered in 50 - 100 cc. amounts.

d. Sedation. The less sedation administered the better. "The best sedative is a cheerful nurse." Pantopon is the narcotic of choice. Patients may require sedation during the induction period. It is suggested that psychotherapy be employed as long as practicable; then, when the patient appears to be becoming too uncomfortable, 22 mgm. of pantopon be given hypodermically and the patient reassured that he soon will feel better. Midway in treatment an additional 11 mgm. of pantopon are occasionally necessary for restlessness. It is urged, however, that a careful distinction be made between restlessness merely because the patient is tired of his position or of the treatment in general, and restlessness on the basis of cerebral edema (see Section IX). Sedation in the latter instance does no good and usually aggravates the symptoms. Only under very exceptional circumstances should a total of more than 32 mgm. of pantopon be administered during treatment. Any drug of the barbituric acid series is contraindicated by reason of furthering cerebral edema.

e. Nutriliment. Many patients complain of hunger throughout the treatment, especially during the noon period. In an effort to alleviate hunger and at the same time to provide readily utilizable foodstuff, the following formulas may be administered routinely:-

(1) Gelatin 2.5 grams	(2) Orange juice 25 c.c.
Water 100.0 c.c.	50% glucose 25 c.c.
	0.3% saline 50 c.c.

The gelatin (Knox's or similar "pure" gelatin) is dissolved in 25 c.c. of cola water. Seventy five c.c. of very hot water are then added, the gelatin is mixed well by stirring, the solution poured over ice chips and administered to the patient in two portions. Two and one half grams of gelatin are given thus every hour during fever. During the forepart of the treatment, four or five 100 c.c. amounts of the orange juice-dextrose-saline mixture are well tolerated; this is given in 30-50 c.c. quantities, not more than 100 c.c. per hour.

f. Surroundings. Many patients enjoy radio music during the treatment; as many, however, object to a radio. During the maintenance period of the fever treatment, relaxation of the patient is often induced if the room is semi-darkened. In general, conversation should be lowered and a conscious effort made to avoid sharp stimuli to the patient by means of loud laughter, banging of doors, dropping objects, etc.

g. Smoking. Since smoking oftentimes has a tendency to induce vomiting during fever therapy, it should be prohibited just before, during, and immediately following the treatment.

VII. DATA OBTAINED DURING FEVER THERAPY:

a. The following information should be charted.

- (1) Temperature, every 15 minutes.
 - (a) The rectal temperature of the patient.
 - (b) The temperature of the cabinet.
- (2) Pulse rate, every 15 minutes.
- (3) Respiratory rate every 15 minutes.
- (4) Blood pressure prior to the treatment and hourly from the end of the induction phase on, and further as indicated by symptoms (see Section IX).
- (5) Fluid intake and output, each on an hourly basis, with the exception of intravenous fluids which are charted as given.
- (6) Sedation.
- (7) Any notes which the nurse-technician considers of interest.

VIII. CARE OF THE PATIENT FOLLOWING FEVER THERAPY:

a. Following termination of the treatment, the patient should be removed from the cabinet to a bed, covered with Turkish towelling or light blanket, and his temperature permitted to drop spontaneously. For one hour following fever, the patient should breathe oxygen continuously by means of a face mask of the BLB type or by a face tent at a rate of 6 liters of oxygen per minute. Any objection to this procedure by the patient should be overruled inasmuch as oxygen at this time makes considerable difference as to how he feels the day following the treatment. The blood pressure is checked shortly after removal from the cabinet and again following the hour of oxygen therapy. Following a bed bath, the patient is removed to his ward. Temperature and blood pressure should be checked every one-half hour until pre-treatment levels have been obtained on two successive occasions. Liquids may be permitted in moderate amounts that evening. Diet and liquids may be given the day following the treatment according to the desires of the patient.

b. Until the post-fever course of the patient is normal, his care is the responsibility of the officer in charge of fever therapy. Any reactions which the patient may exhibit the evening of the day of treatment are to be reported to this officer in addition to the Officer of the Day.

c. Follow-up. The patient will be returned to the referring service as soon as the post-fever course is terminated. All follow-up examinations will be performed by the referring service.

IX. REACTIONS TO FEVER THERAPY:

1. Physically induced fever is a potentially hazardous procedure which carries some danger to the patient. Close cooperation between a well trained physician-nurse team, however, will reduce the dangers inherent in this method of treatment to a point of potentiality rather than of actuality. The responsibility therefore, lies in the training of personnel, not in condemnation of the method of treatment.

2. It should be emphasized that in the overwhelming majority of instances, serious reactions are always preceded by preliminary signs which the alert nurse-technician and medical officer should be able to detect. The prompt recognition of these warning signals and the institution of corrective measures without delay will usually abort the process which may ultimately produce the serious reaction. The following suggestions are designed to aid in the recognition of these premonitory signs of danger:

a. Tetany. This is an occasional complication of the induction period. Early manifestations are: numbness and tingling of the fingers and a feeling of tightness of the orbicularis oris muscle. If uncontrolled, the usual additional signs of typical tetany become evident: carpal spasm, hyperpnea, pedal spasm, positive Chvostek's sign, etc. The intravenous administration of a single dose of 1 gram of calcium gluconate, reassurance, and urging the patient to breathe at his normal even rate of respiration will usually control all such symptoms. It may be necessary to administer sedation at this point to control fear and apprehension. The inhalation of a 10 per cent carbon dioxide - 90 per cent oxygen mixture may be of advantage. Tetany which persists despite these measures will usually necessitate at least temporary cessation of the treatment. Tetany which appears during the maintenance period of fever is of more serious import than during the induction period and the patient should be watched carefully for additional signs of vasomotor imbalance.

b. Vasomotor disturbances. Fever imposes strain on the physiologic balance of the body at three principal points:

- (1) Supply of oxygen to the tissues.
- (2) Maintenance of an adequate blood volume, because of drain of fluid to the sweat glands and the tissue spaces.
- (3) The muscular power of the heart itself, and to a somewhat similar extent, the tonus of the vascular system generally.

A defect at any of these points will ultimately involve the other two, and will produce cerebral edema. During the maintenance period of fever the following indications of vascular instability should be regarded as danger signs and corrective measures promptly instituted:-

- (a) Progressive rise in pulse rate of more than 10 beats per minute, which persists for two 15 minute recordings.
- (b) A sudden, unexplained elevation of pulse rate of 15-20 beats per minute.
- (c) An erratic, fluctuating pulse curve.
- (d) Continuously falling systolic blood pressure (below 90 mm. of mercury).
- (e) Unexplained restlessness which the patient appears unable to control.

- (f) Mental confusion.
- (g) Non-cooperation in a previously cooperative patient.
- (h) Abrupt elevation of temperature above the maintenance level.
- (i) Circumoral pallor and true projectile vomiting suggest cerebral spasm.

c. Visceral damage. Both fever and chemotherapy have been reported to result in damage to one or more of the internal organs, principally the liver. These reactions are delayed and do not appear until some time after therapy. It is in an effort to protect the liver that the liberal use of glucose and the small amount of gelatin that can be demonstrated are recommended.

d. On appearance of one or more of the above signs, the following corrective measures may be of value; the intravenous injection of 50 per cent dextrose; increase of oxygen intake to 8 liters per minute; lowering the patient's temperature by 0.2 - 0.3 degrees F.; icing the forehead of the patient; or the intravenous infusion of bulk fluids. These are intended as suggestions only and are not to supplant the medical officer's clinical estimation of the situation. Heat stroke should never be treated by packing the body of the patient in ice; tepid sponging of the entire body together with fanning the skin surface should be employed.

e. Caution: If at any time during the treatment the condition of the patient does not in general appear to be satisfactory, despite appropriate corrective measures, or in spite of the absence of any specific warning signs, discontinue treatment. It is far safer to subject the patient to a second trial of treatment at a future date than to court the hazards of continuing treatment under such circumstances.

X. RESPONSE TO FEVER THERAPY:

a. Physiologic. The patient usually resumes his normal ward habits within 24 hours following treatment. If vomiting or continued evidence of dehydration persists, the fever therapy medical officer should be called, and additional intravenous fluids may be necessary.

b. Therapeutic. With the treatment method noted under Section VI above, an apparent cure rate of sulfonamide-resistant gonorrhoea of approximately 90 per cent is attained. For the remainder a second similar treatment will cure the majority. A small percentage will be refractory to any reasonable amount of fever-chemotherapy.

APPENDIX E

804 Medical Arts Building
Baltimore, Md.

Dr. O. H. Perry Pepper, Chairman,
Committee on Medicine
University Hospital
Philadelphia, Pa.

April 10, 1943.

Dear Doctor Pepper:-

On March 17, 1943, the Committee on Drugs and Medical Supplies requested the Subcommittee on Venereal Diseases to explore the possibilities of substitutes for arsphenarsen and to transmit our recommendations to that committee. This request was prompted by the current shortage of arsphenarsen manufactured by Parke Davis and Company, and by the fact that two other pharmaceutical houses had prepared for experimental trial, and presumably also for public sale, arsphenarsen substitutes. These are clorarsen, manufactured by E. R. Squibb & Sons, and phenylarsine-dimethane (perhaps alternatively known as arsenoxide-dimethane) manufactured by the Winthrop Chemical Company.

The Subcommittee on Venereal Diseases requested expert advice concerning these two arsphenarsen substitutes from Dr. Harry Eagle. Dr. Eagle prepared a memorandum copies of which are enclosed herewith, which the Subcommittee on Venereal Diseases at its meeting on April 7, 1943, adopted as a portion of its report.

An incomplete bibliography concerning the clinical use of these two arsphenarsen substitutes is as follows:-

- Thompsett, H. K., Downs, H. G., McDermott, W., and Webster, B. The use of clorarsen in the treatment of syphilis. J. Pharmacol. & Exper. Therap. 73: 412, Dec. 1941.
- Long, H. C. Treatment of syphilis with phenarsine hydrochloride. Arch. Derm. & Syph. 47: 226, Feb. 1943.
- Guy, W. H., Golokann, B. A., and Gammann, G. P. Phenarsine hydrochloride in the treatment of syphilis. Arch. Derm. & Syph. 47: 235, Feb. 1943.
- Kampmeier, A. H., Henning, H. B. The treatment of syphilis with clorarsen. Am. J. Syph. Gen. & Ven. Dis. 27: 208, Apr. 1943.

All of the information available to the Subcommittee on Venereal Diseases indicates that clorarsen-Squibb and phenylarsine-dimethane (or arsenoxide-dimethane) become arsphenarsen when dissolved in water and injected intravenously at pH 5 to 7. This being true, the Subcommittee believes that either of these products may be utilized as a satisfactory substitute for arsphenarsen since, in effect, they are arsphenarsen.

Dr. Pepper-2

The Subcommittee on Venereal Diseases suggests to the Committee on Drugs and Medical Supplies that this matter be brought to the attention of the Council on Pharmacy and Chemistry of the American Medical Association, and that the Council be requested to prepare for publication in the Journal of the American Medical Association a statement concerning the interchangeable use of these three chemical products in the treatment of syphilis.

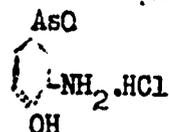
Very truly yours,

S/ J. E. Moore, M.D., Chairman,
Subcommittee on Venereal Diseases.

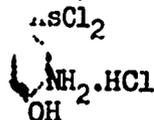
APPENDIX E- (Cont'd)

MEMORANDUM TO THE SUBCOMMITTEE ON VENEREAL DISEASES ON THE
UTILITY OF ARSENEN SUBSTITUTES

arsen is the hydrochloride of 3-amino-4-hydroxy phenylarsine oxide



A solution of the corresponding dichlorarsine



was made

commercially available by May and Baker under the trade name "Halarsol" some twelve years ago, before the development of arsenen. The Squibb preparation "Clorsarsen", and the Winthrop preparation "Phenylarsine-Winthrop", consist of this dichlorarsine, packaged as the dry powder with enough alkali to make a neutral solution.

Electrometric titrations in this laboratory on a dichlorarsine of our own manufacture, as well as the Squibb product, show that when a solution of the dichlorarsine is brought up to pH 5, it is converted quantitatively to the arsine oxide (Table I). In other words, a solution of the dichlorarsine at pH 5 to 7, such as would be used therapeutically, is chemically identical with a solution of arsenen. Provided only that the drugs are used in equivalent amounts, they must give therapeutically the same result. As shown by the data on toxicity in vivo, and spirocheticidal activity in vitro, this has proved to be the case (Table 2). Moreover, since the dichlorarsine has the same toxicity and treponemicidal activity, whether neutralized with NaOH, Na₂CO₃ or Na citrate, it seems clear that the nature of the

base used has no demonstrable effect on the biological activity of the resultant arsine oxide.

From the point of view of therapeutic activity, the several preparations are therefore identical. From the pharmaceutical point of view, the dichlorarsine is perhaps to be preferred. Dichlorarsines in general, and this dichlorarsine in particular, are more stable than the corresponding arsine oxides. To that extent an ampule containing the dry dichlorarsine, with enough dry alkali to make a neutral solution on the addition of water, might be more stable than an ampule of "arsenen"; and the undesirable chemical changes sometimes noted in arsenen ampules, evidenced by the discoloration of the powder, and believed to be due to oxidation of the aminophenol grouping, might thus be avoided or minimized.

(Tables I and 2 follow)

Table 1

Titration of 3-amino (hydrochloride) -4-OH
phenylchlorarsine

Compound tested	pH on addition of indicated # of equivalents				
	1	2	3	3-1/4	3-1/2
12/16/40 Sy hills research Lab'y n-10	1.4	2.3	4.75	5.6	7
1/27/41 Squibb Chlorarsen	1.46	2.3	4.85	5.7	7

Conclusion: Compound is present as phenylarsine oxide in solution at
pH 5.0.

Table 2

Compound tested	L.D. 50 mg/kg	Water toxicity	Molar toxicity, nematicidal activity in vitro
"K. Larson"	42.6	6.94	38.2
3-NH ₂ -4-OH phenyldi- chlorarsine hydro- chloride	48.2	6.93	36.2

Compound prepared in this laboratory and neutralized with NaOH.

Sy hills research Laboratory
U.S. Public Health Service
Johns Hopkins Hospital
Baltimore, Md.

April 5, 1943.

S/ Harry Eagle, M.D., Surgeon.

NOT FOR PUBLICATION

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Indexed

MINUTES OF THE SEVENTEENTH MEETING OF THE

SUBCOMMITTEE ON VENEREAL DISEASES - NATIONAL RESEARCH COUNCIL

December 1, 1942

~~NOT FOR PUBLICATION
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NATIONAL RESEARCH COUNCIL~~

The seventeenth meeting of the Subcommittee on Venereal Diseases was held at the National Academy - Research Council Building, Washington, at 10:00 A.M. on Tuesday December 1, 1942. Present were the following:

From the Subcommittee on Venereal Diseases Dr. J. E. Moore, Chairman, Doctors John H. Stokes, Walter Clarke, Russell Herrold, Oscar Cox and Nels Nelson. Doctor John Mahoney was absent.

From the National Research Council Doctors Lewis Weed, O. H. Perry Pepper, E. H. Cushing, George A. Carden, Jr, and T. R. Forbes.

From the U. S. Army Brigadier General H. C. Coburn, Colonel James Simmons, Lieut. Colonel T. B. Turner, Lieut. Colonel Roger Prentiss, Major Thomas H. Sternberg, Major G. W. Anderson, Captain Robert H. Riedel.

From the U. S. Navy, Lieutenants George W. Mast, I. M. Kruger, J. F. Shrontz, and Surg. Cmdr. R. W. Mussen, R.N., British Naval Medical Liaison Officer.

From the U.S. Public Health Service Doctors Harry Eagle, Austin Deibert, and L. J. Hanchett.

And in addition and by invitation Dr. C. Phillip Miller, University of Chicago.

There was submitted to the committee for approval certain recommendations on the prevention of venereal disease in female personnel of the Womens Army Auxiliary Corps. These recommendations were based on a report by the Subcommittee of a conference on this subject, the meeting of the Subcommittee having been held in Washington on August 3 and 4, 1942, the Minutes of the meeting having been previously circularized. These Minutes were considered in connection with the Minutes of the first meeting of the conference on the same subject, held on July 23, which eventuated in certain recommendations approved by the Subcommittee on Venereal Diseases on July 24 and by the Committee on Medicine on July 25, 1942. A considerable discussion ensued regarding these recommendations which were both simplified and amended by the Subcommittee on Venereal Diseases, as indicated in the following letter of transmissal to the Committee on Medicine.

December 4, 1942.

Dr. O. H. Perry Pepper, Chairman,
Committee on Medicine,
University Hospital
Philadelphia, Penna.

Dear Doctor Pepper:

At a meeting of the Subcommittee on Venereal Diseases, National Research Council on December 1, 1942, a series of recommendations concerning the pre-

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vention of venereal disease in female personnel of the Women's Army Auxiliary Corps were passed. These recommendations are supplementary to those previously passed and approved by the Subcommittee on Venereal Diseases on July 24, 1942, and by the Committee on Medicine the following day. Among these previously approved recommendations (July 24, 1942) were the following:

THAT A SUBCOMMITTEE OF THIS CONFERENCE (i.e., specially appointed Conference on the prevention of venereal disease in the WAAC. Conferees: Dr. Mary S. Fisher, Vassar College, Poughkeepsie, N.Y. Dr. Ernest Groves, University of North Carolina, Chapel Hill, N.C. Dr. Bertha M. Shafer, Northwestern University Medical School, Chicago. Dr. Raymond Squier, Columbia University Medical School, New York. Dr. Edward L. Keyes, Tuxedo, N. Y. Dr. Margaret Barnard, New York City Health Department, and Dr. Bessie Moses, Johns Hopkins University) BE APPOINTED BY THE CHAIRMAN (Dr. J. E. Moore) TO PREPARE FOR THE USE OF THE WOMEN'S ARMY AUXILIARY CORPS OUTLINES OF LECTURES OF PAMPHLET MATERIAL (on sex hygiene and venereal disease).

The Chairman appointed such a subcommittee of the Conference consisting of Doctors Fisher, Groves, Shafer, Squier, Keyes, and Moore, which met in Washington August 3 and 4, 1942, and which drew up various recommendations. These, as amended and approved on December 1, 1942, by the Subcommittee on Venereal Diseases are as follows:-

I. THAT EDUCATION OF PERSONNEL OF THE WAAC IN SEX HYGIENE AND VENEREAL DISEASE BE MADE PART OF A GENERAL EDUCATIONAL PROGRAM OF HYGIENE AND HEALTH.

II. THAT A MINIMUM BASIC TRAINING COURSE OF TEN HOURS ON SEX HYGIENE AND THE PHYSIOLOGY OF REPRODUCTION, INCLUDING THE PREVENTION OF VENEREAL DISEASE, BE REQUIRED AS EARLY AS POSSIBLE IN ALL TRAINING COURSES FOR OFFICERS OR ENLISTED PERSONNEL, WHITE AND COLORED; AND THAT INFORMATION AS TO CONTRACEPTION BE OFFERED ON A VOLUNTARY BASIS TO THOSE WHO DESIRE IT.

It was suggested by the Subcommittee of the Conference, and approved by the Subcommittee on Venereal Diseases that the ten hours to be required as basic training be divided as follows:-

- 1st hour- Lectures on sex hygiene, outline and text prepared by Dr. Ernest Groves
- 2nd hour- Lectures on basic facts of individual psycho-sexual development, prepared by Dr. Mary S. Fisher.
- 3rd and
- 4th hours- Illustrated lectures on the anatomy and action of sex, prepared by Dr. Raymond Squier.
- 5th and
- 6th hours- Lectures on the prevention and control of the venereal diseases, prepared by Dr. Bertha M. Shafer.
- 7th and
- 8th hours- Question and discussion periods. The Conference suggested that written questions be called for at the end

of such lecture period, with planted questions included, these to be inserted, answered, and discussed during the question and discussion periods.

- 9th hour- Written examination on content of lectures and pamphlets.
- 10th hour- Summarizing discussion and correction of persistent erroneous ideas.

The reasons for the written examination are included in the third and fourth recommendations prepared by the Subcommittee of the Conference, and approved by the Subcommittee on Venereal Diseases, as follows:-

III. THAT A WRITTEN EXAMINATION OF THE TRUE-FALSE AND COMPLETION TYPE BE REQUIRED ON ALL MATERIAL COVERED, PARTICULARLY THE BASIC FACTS OF THE PHYSIOLOGY OF SEX RELATIONSHIPS AND VENEREAL DISEASE, AT THE END OF THE MINIMUM TEN HOUR COURSE.

IV. THAT SUCH AN EXAMINATION BE USED TO INDICATE HOW MUCH TRAINING OR REVIEW SHOULD BE GIVEN TO GUARANTEE MASTERY OF THE NECESSARY FACTS AND INFORMATION.

It was felt that the written examination given to early groups so instructed would be valuable in orientation as to the amount of training required for subsequent groups.

The Subcommittee of the Conference prepared the outlines of lectures enumerated above and these, four in number (1. Sex Hygiene. 2. Basic Facts of Individual Psycho-Sexual Development. 3. The Anatomy and Action of Sex. 4. The Prevention and Control of Venereal Diseases), were submitted to the Subcommittee on Venereal Diseases which recommended:-

V. THAT THESE LECTURES BE SUBMITTED TO THE SURGEON GENERAL U. S. ARMY, AND THAT THEY BE UTILIZED FOR THE WAAC, SUBJECT TO EDITING BY THE SURGEON GENERAL'S OFFICE AND BY THE DIRECTOR WAAC.

Copies of these lectures are appended hereto as Appendix "A".

In accordance with the recommendations previously approved on July 24th, a proposed pamphlet for distribution to the WAAC was submitted to the Subcommittee on Venereal Diseases. It was recommended that:

VI. THIS PAMPHLET BE PREPARED FOR DISTRIBUTION TO WAAC PERSONNEL.

A draft of it is enclosed as Appendix "B".

In planning the minimum training course as given above, the Conference took cognizance of the following facts:

- a) Intellectual understanding and emotional acceptance of objective and scientific facts are not necessarily correlated in the field of sex hygiene.

- b) The chief difficulties in the successful completion of such a course lie in the fears, resistances and emotional immaturity of the majority of women, regardless of intelligence and educational background.
- c) Major factors in bringing intellectual understanding and emotional acceptance closer together through the medium of such a course are:-
 - 1) The fact of official recognition of the importance and universality of problems of sex hygiene is reassuring to most individuals.
 - 2) Scientific and objective discussion of the facts and problems of sex hygiene in large groups in itself makes individual acceptance and understanding easier.
 - 3) Provision for objective and anonymous discussion of individual questions raised by the group is of the greatest importance in determining how much of what has been "learned" has been understood and applied.
 - 4) Provision for a continuous individual counseling service is of basic importance in preventing loss of efficiency and lowering of morale, due to anxiety, fear, or guilt.
(Note: It is not expected that all medical officers will be competent advisers in the field of sex hygiene, but every attempt should be made to train medical and line officers to recognize problems and to provide competent referral or consultation service when indicated.)

It was further recommended and approved by the Subcommittee on Venereal Diseases:

VII. THAT ITINERANT LECTURERS, PREFERABLY EDUCATORS SPECIALLY TRAINED IN THIS FIELD, GIVE THE INTRODUCTORY LECTURES ON SEX HYGIENE AND THE FACTS OF INDIVIDUAL PSYCHO-SEXUAL DEVELOPMENT.

VIII. THAT FOR THE REMAINDER OF THE INSTRUCTION SPECIALLY QUALIFIED MEDICAL OFFICERS BE SELECTED ON THE BASIS OF THE FOLLOWING CRITERIA:

1. Previous interest and experience in the field of sex hygiene, as illustrated by work in maternal health clinics, should be required.
2. Married physicians preferred.
3. Total personality adjustment considered to be of greatest importance, including ability to discuss facts of sex hygiene sympathetically, objectively, and scientifically.

IX. THAT THE WHOLE QUESTION OF SEX HYGIENE BE REOPENED AT FREQUENT INTERVALS AFTER THE COMPLETION OF THE BASIC TRAINING COURSE, IN THE FOLLOWING WAYS:

1. Distribution of new pamphlets
2. Showing of moving pictures
3. Supplementary lectures.

X. THAT A COUNSELING SERVICE ON QUESTIONS OF PERSONAL SEX HYGIENE BE CONSIDERED BASIC TO THE MORALE, HEALTH, AND EFFICIENCY OF EACH UNIT.

XI. THAT PRODUCTION OF A SOUND MOTION PICTURE OR PICTURES DEPICTING THE PHYSIOLOGY OF REPRODUCTION AND MENSTRUATION, AND THE PREVENTION OF VENEREAL DISEASES, BE UNDERTAKEN TO BE USED AS PART OF THE BASIC TRAINING COURSE FOR THE WAAC.

XII. THAT A BOOKSHELF OF SELECTED BOOKS IN THE FIELD OF SEX HYGIENE BE STANDARD EQUIPMENT IN ALL LIBRARIES ATTACHED TO TRAINING CENTERS.

These recommendations are submitted for the approval of the Committee on Medicine and, if approved, for forwarding to the Surgeon General, U. S. Army.

Very truly yours,

S/ J. E. Moore, M.D., Chairman
Subcommittee on Venereal Diseases.

The drafts of the several lectures and of the pamphlet referred to in this letter have already been circularized, and are therefore not appended herewith.

The Chairman then reported on the Minutes of a conference on biologic false positive serologic tests for syphilis, held at the National Research Council on August 13, 1942, and of the subsequent conference held in New York and in Chapel Hill, N.C. on September 2nd and Sept. 4th, 1942. As a result of these conferences the Chairman reported that proposals for OSRD contract on this subject have been made, and approved, by Doctors Beard and Neurath at Duke University, and by Doctors Moore and Kabat, Columbia University; and the Surgeon General, U. S. Public Health Service has assigned to the latter project the services of Dr. Bernard Davis, U.S. Public Health Service. The Minutes of these conferences have been previously circularized and are therefore not appended herewith.

The Chairman then reported on the Minutes of a conference on chemical prophylaxis held at the National Research Council on November 18, 1942. The Minutes of this conference are appended hereto as "Exhibit A." On the basis of this conference the Subcommittee on Venereal Diseases recommended that:

A COMMITTEE BE APPOINTED TO DRAW UP AN ORGANIZED PLAN OF ATTACK ON THE PROBLEM OF CHEMICAL PROPHYLAXIS AND TO INDICATE TO PRESENT AND POTENTIAL OSRD CONTRACT HOLDERS THE MOST IMMEDIATE PROFITABLE LINES OF INVESTIGATION FOR THEMSELVES TO FOLLOW.

The Chairman also reported that on the basis of this conference a proposal for OSRD contract had been made, and approved by the Committee on Medical Research, by Dr. Herbert O. Calvery, Chief, Division of Pharmacology, Food and Drug Administration, for "Pharmacologic and toxicologic investigation of venereal prophylactics with reference to (1) Absorption through skin and mucous membranes, (2) surface active agents (wetting agents, detergents, etc.) and their influence on absorption when compounded with such prophylactics."

The Chairman then reported on the action taken by the Committee on Medicine at its meeting on October 16, 1942, on the subject of intensive arsenotherapy. The pertinent portions of the Minutes of the Committee on Medicine were read. The Committee on Medicine reiterated the recommendation originally made by the Subcommittee on Venereal Diseases on January 13, 1942, and approved by the Committee on Medicine on February 17.

The Chairman then read certain correspondence from groups of California investigators offering their services in research associated with the war effort. Dr. Pepper reported that no action on this correspondence was necessary since the Committee on Medical Research had already invited two persons from the California group to come to Washington to survey the manners in which these groups may be of service.

The Chairman next read to the Subcommittee certain correspondence between himself and Dr. A. N. Richards, Chairman, Committee on Medical Research, concerning surveys of existing projects sponsored by this Subcommittee. Likewise the Chairman reported in brief on the recommendations made by him, as consultant to CMR concerning these projects.

As a result of consideration of this correspondence, the Chairman was directed to write to Dr. Richards to the effect that the avenues of investigation of particular interest to the Subcommittee on Venereal Diseases, in addition to studies on intensive arsenotherapy of syphilis, on the prophylaxis of venereal disease, and on biologic false positive serologic tests for syphilis, included the following:-

FURTHER STUDIES IN THE DIAGNOSIS AND TREATMENT OF GONORRHEA.

In a letter to Dr. Richards the Chairman had commented on the complicated existing machinery which deals with OSRD contracts, and desirable methods of expediting their consideration. As a result of this comment it was moved and passed that:-

FUTURE PROPOSALS FOR OSRD CONTRACT BE SUBMITTED BY THE CHAIRMAN SUBCOMMITTEE ON VENEREAL DISEASES FOR APPROVAL TO THOSE MEMBERS OF THE COMMITTEE ON MEDICINE WHO MAY BE PRESUMED TO HAVE SPECIAL TECHNICAL KNOWLEDGE OF THE PARTICULAR PROPOSAL IN QUESTION, AND THAT ACCEPTANCE AND RATING OF THE PROPOSAL FOR CONTRACT BE BASED UPON THE OPINION OF THE CHAIRMAN AND OF THE SELECTED MEMBERS OF THAT COMMITTEE.

It was likewise recommended that:

PROPOSALS FOR EXTENSION OF CONTRACT BE HANDLED IN THIS SAME MANNER.

The proposal for extension of contract OEM-cnr-34 by Doctors Schoch and Alexander in the amount of \$13,120. was accepted and rated "A".

The proposal for contract by Dr. Earle R. Caley, Wallace Laboratories, New Brunswick, New Jersey, for "Chemical and biological evaluation of surface active agents in order to increase the scope and efficacy of topical medication and prophylaxis" was considered and rejected.

There was next considered certain correspondence from Dr. F. V. Sander, Ortho Products, Inc., Linden, New Jersey, offering the cooperation of the laboratories of this company in studies on chemical prophylaxis. The Subcommittee voted to authorize the Chairman to visit Dr. Sander's laboratory at the earliest practicable date and to report further.

There was next considered a series of letters relating to proposed human experimentation in gonorrhea, and in particular letters from Dr. Charles M. Carpenter, University of Rochester, Rochester, New York, and Dr. Alfred Cohn, New York City Health Department, requesting approval of such projects tentatively designed to be carried out in the prisons of Georgia and of New York State. In this connection the Chairman reported that at the previous conference on chemical prophylaxis such human experimentation had been regarded as highly desirable. He was directed by that conference to write to the Surgeons General, U. S. Army, Navy, and Public Health Service, requesting approval in principle of this type of experimentation. To date letters have been received from the Surgeon General, U. S. Public Health Service to Dr. Lewis Weed, Chairman, Division of Medical Sciences, National Research Council, and from the Surgeon General, U. S. Navy, to Dr. Charles M. Carpenter, approving of such experimentation. In the meanwhile the Chairman reports that the Surgeon General U. S. Navy has been requested to readdress his letter to Dr. Weed, and a request for such a letter is now pending in the Office of the Surgeon General U. S. Army.

A full discussion of all of this material ensued, as a result of which it was recommended:-

THAT HUMAN EXPERIMENTATION IN THE PROPHYLAXIS OF GONORRHEA IS DESIRABLE IN PRISON INMATES THROUGH THE COOPERATION OF STATE AUTHORITIES. THE CHAIRMAN, SUBCOMMITTEE ON VENEREAL DISEASES, SHALL BE AUTHORIZED (if this recommendation is approved by NRC, CNR and OSRD) TO APPROACH THE RESPONSIBLE AUTHORITIES IN SELECTED STATES WITH A VIEW TO THE CARRYING OUT OF SUCH EXPERIMENTATION BY RESPONSIBLE PHYSICIANS ACTING UNDER OSRD CONTRACTS. THE DETAILS OF SUCH EXPERIMENTATION AND ITS RISKS SHOULD BE DRAWN UP BY A CONFERENCE, THE PERSONNEL OF WHICH SHALL BE SELECTED BY THE CHAIRMAN SUBCOMMITTEE ON VENEREAL DISEASES. THE PROPOSALS OF DR. CHARLES M. CARPENTER, ROCHESTER, NEW YORK, AND ALFRED M. COHN, NEW YORK CITY, INFORMALLY SUBMITTED TO THE SUBCOMMITTEE ON VENEREAL DISEASES ON DECEMBER 1, 1942, SHALL BE APPROVED IN PRINCIPLE SUBJECT TO QUALIFICATIONS ARRIVED AT BY THE CONFERENCE AUTHORIZED ABOVE.

It was suggested that the personnel of such a conference should include

Dr. J. E. Moore, Chairman, Dr. G. H. P. Pepper, Chairman Committee on Medicine, Dr. R. A. Vonderlehr, Assistant Surgeon General, U.S. Public Health Service, Dr. Lowell J. Reed, Johns Hopkins School of Hygiene and Public Health, Doctors Oscar Cox and Russell Herrold from the Subcommittee on Venereal Diseases, Doctors Carpenter and Cohn who have made proposals for such human experimentation, representatives of the States of Georgia and New York, to be designated respectively by Doctors Carpenter and Cohn, as being the States in which such experimentation is at present planned, and representatives of the Surgeons General, U. S. Army and Navy.

The Chairman next presented to the Subcommittee certain correspondence from Doctors J. Murray Luck, Hubert S. Loring, and Sidney Raffel, Stanford University, Palo Alto, California, proposing tentatively to undertake certain experiments on the basis of an OSRD contract on the subject of biologic false positive serologic tests for syphilis. This correspondence had also been sent in duplicate to Dr. Harry Eagle, U.S. Public Health Service, who has informally acted as advisor to the Chairman Subcommittee on Venereal Diseases in this respect. The Subcommittee agreed that Dr. Eagle might answer the letter from Doctors Loring and Raffel to the effect that if an OSRD contract is essential for the work proposed by them, it would probably be better to await the outcome of preliminary experiments now under way in the laboratories of Doctors Neurath and Beard at Duke University and of Kabat, Moore and Davis at Columbia. It was felt that if these studies offered no promising approach to the practical problem of differentiating syphilitic from biologic false positive reactions, the avenues of study outlined by Doctors Loring and Raffel should be given all possible support.

The Chairman then read certain correspondence between himself and Dr. A.L. Tatum, University of Wisconsin, Madison, Wisconsin, in which Dr. Tatum offered to place himself and his laboratory at the disposal of the Government for the prosecution of studies in which the Subcommittee on Venereal Diseases is interested. It was moved that Dr. Tatum be authorized to come east for a conference with the Chairman.

The Chairman then read certain correspondence with Dr. Murray Sanders, Columbia University, New York, in which it was indicated that Dr. Alwin Pappenheimer, Department of Pathology, Columbia University, might be associated with the group of investigators working on chemical prophylaxis in respect of a study of lymphogranuloma as a local infection in guinea pigs. The Chairman was directed to approach Dr. Pappenheimer in this respect.

There was then considered a tentative proposal from Dr. Frank Combes for a supplementary appropriation on his existing contract in the amount of \$390. monthly. Dr. Combes' letter was not clear. It appeared (a) that he wished to utilize these funds, at least in part, for a further study of the value of intravenous Frei testing in lymphogranuloma, and that in probable pursuit of this problem he wished to place Dr. Orlando Canizares on full time at \$300. a month. In these respects the Chairman reported that as consultant to CMR he had recommended that Dr. Combes and his associates drop the problem of intravenous Frei testing in lymphogranuloma as of little or no value to the armed forces. The Subcommittee by vote upheld the Chairman in this stand. The Chairman likewise reported that if Dr. Combes and his associated limited their proposal for contract to a continued study of the prophy-

laxis of chancroid, the only portion of the contract likely to prove of immediate value to the armed forces, it was not clear that the full time of Dr. Canizares could be profitably so employed. The Chairman was directed to write to Dr. Combes to this effect.

The Chairman next reported that he had written to Dr. Katharine Anderson, Vanderbilt University Hospital, Nashville, Tennessee, concerning the applicability of her method of chancroidal infection of the chick embryo to the study of chemical prophylaxis; but that no reply had as yet been received. ✓

There then ensued a further discussion of the subject of chemical prophylaxis as a result of which the Subcommittee recommended:

THAT AS EARLY AS POSSIBLE IN JANUARY 1943 THERE BE HELD AT THE LABORATORY OF DOCTORS COHN AND CARPENTER, UNIVERSITY OF ROCHESTER, ROCHESTER, NEW YORK, A FURTHER CONFERENCE ON THE SUBJECT OF CHEMICAL PROPHYLAXIS WITH THE IDEA OF ALLOCATING VARIOUS PHASES OF THE PROBLEM TO INVESTIGATORS ATTENDING THIS CONFERENCE. IT WAS SUGGESTED THAT THE CONFERENCE SHOULD INCLUDE -

From the Subcommittee on Venereal Diseases: Dr. J.E. Moore, Dr. J.F. Mahoney, Dr. Russell Herrold, and Dr. Oscar Cox;

The following OSRD contract holders: Drs. Harry Eagle, Justina Hill, Geoffrey Rake, Orlando Canizares, Stafford Warren, C. M. Carpenter, H. O. Calvery, and Marvin Thompson

The following persons whose collaboration may be enlisted: Dr. Alwin Pappenheimer, New York, Dr. A. L. Tatum, Madison, Wis., Dr. Phillip Miller, Chicago, Dr. Austin Deibert, U.S. Public Health Service, Hot Springs, Ark., Dr. Alfred Cohn, New York, Dr. Richard Greenblatt, Augusta, Ga., and possibly Dr. W. A. Fleming, Chapel Hill, N.C;

And, in addition, representatives of the Surgeons General, U.S. Army and Navy.

It is hoped that approval may be had for this conference to be held in Rochester, rather than in Washington, in part to provide opportunity for the conference to inspect the work of Doctors Carpenter and Warren.

There then ensued a general discussion of the twin problems of sensitization of the sulfonamides and of the possible effect of these drugs on muscular coordination, and the relationship of each of these points to their use in local or oral chemical prophylaxis. The Chairman read certain correspondence between himself and various investigators on these points, and reported briefly on certain work just completed by Lieutenant Frank Reynolds, U.S.N., and Dr. Frank Walsh, Wilmer Ophthalmological Institute, on the effect of sulfathiazole and sulfadiazene on visual efficiency. The Subcommittee agreed that the paper by Reynolds and Walsh should be submitted to the Committee on Aviation Medicine. The Subcommittee also authorized the Chairman to investigate further the possibilities for research studies in these two fields by civilian or military agencies.

✓ Finally the Chairman read certain correspondence with Mr. Joe Brodigan, Brooklyn, New York, offering to cure venereal disease of any type or severity by the use of pus suspended in strong coffee. No action was taken on Mr. Brodigan's proposal. The Chairman regrets to announce that subsequent to the meeting of the Subcommittee on Venereal Diseases, and as a result of a speech made by Vice President Wallace in Chicago, Mr. Brodigan has now withdrawn his offer to the armed forces. Following further facetious comments on Mr. Brodigan's proposal, the meeting adjourned.

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MINUTES OF THE SIXTEENTH MEETING OF THE
SUBCOMMITTEE ON VENEREAL DISEASES - NATIONAL RESEARCH COUNCIL

July 24, 1942.

The sixteenth meeting of the Subcommittee on Venereal Diseases was held at the National Academy - Research Council Building, Washington, at 10:00 A.M. on Friday, July 24. Present were the following:

From the Subcommittee on Venereal Diseases, Dr. J. E. Moore, Chairman, Doctors Stokes, Cox, Nelson, Mahoney, Clarke, and Herrold.

From the National Research Council, Doctors Weed, Cushing, Larkey, Forbes, and Carden.

From the U. S. Army Lieut. Col. Turner, Prentiss; Majors Brunfield, Anderson, and Shull.

From the U. S. Navy Capt. Stephenson and Lieut. Mast.

From the U. S. Public Health Service Passed Asst. Surgeon Otis Anderson.

The Subcommittee considered first the Minutes of a Conference on the prevention of venereal disease in female personnel of the Women's Army Auxiliary Corps, held at the National Research Council in Washington on the preceding day, July 23. These Minutes, as amended by the Subcommittee are appended hereto as Exhibit A. These Minutes as a whole were approved, and specifically there were approved eleven recommendations, which appear in the Minutes as indented and capitalized paragraphs.

The Subcommittee then considered the following proposals for OSRD contracts.

The proposal of Dr. C. Phillip Miller, University of Chicago, for a study of "Prophylaxis of experimental gonococcal infection", was rejected.

The proposal of Dr. Theodore Rosebury for "A comparative study of the morphology and motility of *Treponema pallidum* and commensal spirochetes under darkfield illumination by means of motion pictures" was rejected.

The proposal of Dr. Marvin R. Thompson, Warner Institute, for therapeutic research, for "(1) Chemoprophylaxis of gonorrhea, lymphogranuloma, and chancroid; and (2) A study of the sulfonamides in ointment bases" was accepted and rated A. The vote on this proposal was six to accept and rate A, and one to reject.

The Chairman reported on certain matters held over from the Minutes of the previous meeting, particularly with regard to biologic false positive serologic tests for syphilis.

At the previous meeting the chairman was authorized to correspond with Dr. Mary Pangborn, New York State Health Department Laboratories, with regard to the possibility of Dr. Pangborn's furnishing to certain other laboratories a supply of "cardiolipin", the supposed active principle of tissue extract antigens isolated by Dr. Pangborn. The chairman reported that he had done so, that Dr. Pangborn had referred the correspondence to her chief, Dr. Augustus Wadsworth, and that Dr. Wadsworth had replied that his laboratory was unable to collaborate in this respect at the present time.

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At the previous meeting the chairman was likewise authorized to correspond with certain physical chemists as to the possibility of the identification and differentiation of syphilis reagin from the reagin or reagin-like substance occurring in the blood of normal persons, or in those suffering from diseases other than syphilis. The chairman reported that he had so corresponded with Doctors Edwin J. Cohn of Harvard University, J. Murray Luck of Stanford University, E. A. Kabat of Columbia University, and William Welker of the University of Illinois. Correspondence to and from these investigators was read. This correspondence indicated that certain promising leads in the differentiation of syphilitic and non-syphilitic reagin might perhaps be arrived at by collaboration between physical chemists, serologists, and clinicians. On the basis of the general discussion which followed and of additional emphasis on the importance of biologic false positive serologic tests to the Armed Forces (certain excerpts from the Minutes of the Canadian National Research Council were at this point discussed, and the Army and Navy officers present reiterated their previously expressed opinion that biologic false positive tests were particularly important to the Services, because of the punitive and compensation difficulties which might arise in the case of erroneous diagnosis of syphilis), the Subcommittee voted to authorize a further conference on the subject of biologic false positive tests. Conferees were tentatively named as Doctors Cohn, Luck, and Kabat, named above; and in addition Dr. Duncan MacInnes of the Rockefeller Institute for Medical Research, Dr. Foster Kendall of the Welfare Laboratories, Welfare Island, New York, Dr. Harry Eagle of the U.S. Public Health Service; and from the Subcommittee on Venereal Diseases, Doctors Stokes, Mahoney, and Moore. The date for such a conference was tentatively set as August 13, 1942.

There being no further business, at 5:00 P.M. the meeting adjourned.

EXHIBIT A

~~CONFIDENTIAL~~

MINUTES OF A CONFERENCE ON THE PREVENTION OF VENEREAL DISEASE IN
FEMALE PERSONNEL OF THE WOMEN'S ARMY AUXILIARY CORPS HELD AT
THE NATIONAL RESEARCH COUNCIL IN WASHINGTON July 23, 1942
AS AMENDED AND APPROVED AT A MEETING OF THE SUBCOMMITTEE
ON VENEREAL DISEASES, NATIONAL RESEARCH COUNCIL
July 24, 1942

The authorization for this conference is provided in the following correspondence:

"Dr. Lewis H. Weed, Chairman
National Research Council

July 7, 1942

Dear Doctor Weed:

The recent authorization by Congress of the formation of the Women's Army Auxiliary Corps with an anticipated strength of 150,000 has brought to the attention of The Surgeon General's Office problems related to the prevention of venereal disease in female personnel. The Surgeon General directs me to request that the appropriate committee of the National Research Council consider this question with a view to giving this office the benefit of its advice in the matter.

Very sincerely yours,

S/ James S. Simmons,
Colonel, Medical Corps,
Assistant."

"Dr. J. E. Moore
Chairman, Subcommittee on Venereal Diseases
Baltimore, Maryland

July 13, 1942

Dear Doctor Moore:

The Surgeon General of the Army has requested the Division of Medical Sciences, National Research Council, to consider the question of the prevention of venereal diseases in regard to the Women's Army Auxiliary Corps. This request has been referred to the Subcommittee on Venereal Diseases of the Division of Medical Sciences, National Research Council, and a conference group of those cognizant of the problem has been established. It is hoped that you will be able to serve as chairman of this group.

Yours very sincerely,

S/ Lewis H. Weed, Chairman,
Division of Medical Sciences."

Pursuant to this authorization a conference was held at the National Academy of Sciences, Washington, D.C., on July 23, 1942. Present were the following:

Conferees:

Dr. Margaret Barnard, New York City Health Department; Dr. Mary Fisher, Vassar College, Poughkeepsie, N. Y.; Dr. Ernest Groves, University of North Carolina, Chapel Hill, N.C.; Dr. Bessie Moses, Johns Hopkins University, Baltimore, Md.; Dr. Bertha M. Shafer, Northwestern University Medical School, Chicago, Ill.; and Dr. Raymond Squier, Cornell University Medical School, New York.

From the Subcommittee on Venereal Diseases, National Research Council:
Dr. C. Walter Clarke, and Dr. J. E. Moore, Chairman of this conference.

From the National Research Council: Drs. E. H. Cushing, Sanford Larkey, and Forbes.

From the United States Army: Lieut. Colonels R. G. Prentiss, and T. B. Turner from the Office of the Surgeon General; Lieut. Col. H. P. Tasker from Headquarters W. A. A. C., and Majors H. J. Shull, W. A. Brumfield, and G. W. Anderson from the Office of the Surgeon General.

From the United States Navy: Capt. C. S. Stephenson, and Lieutenants G. W. Mast, C. W. Churchill, F. W. Reynolds, and J. F. Shrontz from the Office of the Surgeon General, and Miss Elizabeth P. Taylor (Civilian consultant Navy Women's Reserve Corps), representing Miss Mildred McAfee, the proposed Director of that Corps, if and when authorized.

Also present were Miss Roberta Zechiel, Audio Productions, Inc., 630 Ninth Avenue, New York, a script writer for Navy motion pictures, and Mr. Morris Ernst, the legal adviser of the Planned Parenthood Federation of America.

It was pointed out that the deliberations of this Conference applied only to the W. A. A. C. of the U. S. Army, since the formation of the analogous Corps in the U. S. Navy has not yet been authorized. Nevertheless, it was felt by Captain Stephenson that the deliberations of the Conference might be of value to the W. N. R. C., if and when authorized. It was further brought out that the Acts of Congress establishing the two Corps differ in that the W. A. A. C., being auxiliary, serves with and not in the U. S. Army, whereas the proposed W.N.R.C. will be an integral part of the U. S. Navy.

The Chairman of the conference then opened a general discussion by reading certain documents relative to the experience of the British Women's Auxiliary Services, particularly the ATS (Auxiliary Territorial Service), based on observations of an American woman physician, Dr. Sarah Bowditch, especially trained in the venereal disease field, who had just returned from Great Britain after a year of service there with the American Red Cross Emergency Service. There was also read into the record certain experience of the Canadian Women's Auxiliary Corps, especially relating to the RCAF, based on a report to Capt. C. S. Stephenson, U. S. Navy. These reports indicated that in the Women's Auxiliary Corps of the British and Canadian Armies the problems of venereal disease and of pregnancy are major ones which present serious difficulties in their management.

The Chairman then offered an estimate based on conversations with civilian and Army physicians experienced in the field, that the problems of venereal disease in the Women's Army Auxiliary Corps might be divisible into three groups on the basis of the type of personnel: a) officers; b) white enlisted personnel; c) Negro enlisted personnel. It may be anticipated that American experience will repeat the British and Canadian. It was suggested that under the stress of war time the probable exposure rate of female personnel could be estimated on an over-all basis in approximately the same fashion as the exposure rate for male personnel. With men of the Armed Forces it is roughly estimated that 15 per cent will expose themselves repeatedly, regardless of all effort to the contrary; that 15 per cent will never do so, regardless of temptation; and that 70 per cent may be expected to expose themselves occasionally under the stress of extraneous circumstances, such as emotion, alcohol, etc. With women of the W. A. A. C. the guess was hazarded that these proportions might be roughly: 5 per cent who would expose themselves repeatedly, regardless of hazard; 45 per cent who would not risk exposure under any circumstances; and 50 per cent who would be occasionally but not promiscuously exposed under circumstances similar to those involving male personnel. After some discussion of this estimate, it was felt by certain members of the conference, notably Dr. Groves, that the proportion of women who might be expected to expose themselves occasionally to the risk of venereal disease or pregnancy would, on an over-all basis, probably be considerably higher than 50 per cent.

The Conference agreed that with women, as with men, the best preventive of venereal infection is continence; and that every effort should be made with W. A. A. C. personnel, through all available channels (Chaplain's Corp, Medical Corps and line officers) to foster the feasibility and desirability of continence. Stress should be laid upon this topic not only from sociologic, familial, and personal points of view, but also from the standpoint of military efficiency and conservation of woman power. Nevertheless the Conference recognizes that none of these appeals will be effective under certain conditions; and that realism requires the adoption of medical protective measures when other considerations fail. The Conference believes further that such medical measures should be directed particularly toward the larger group of W. A. A. C. personnel who are neither habitual offenders nor total abstainers, but whose military careers may be endangered by single or infrequently repeated exposures.

The Conference then discussed the relation of the venereal disease problem to that of pregnancy. It was agreed, after expression of opinion by members of the Conference and by the Army and Navy officers present, that these two problems are inextricable; and that this Conference and subsequently the Subcommittee on Venereal Diseases might properly concern themselves with the problems of pregnancy and of contraception.

The Conference then agreed that the major problems confronting the W. A. A. C. are the prevention of venereal disease and the prevention of pregnancy rather than the medical care of these conditions if and when they develop. In this connection the character of medical service to be available to the W. A. A. C. seemed to the Conference to be of importance. The medical care of the W. A. A. C. is a responsibility of the Surgeon General, U. S. Army. It seemed to the Conference desirable that to some extent, at least, women physicians should serve with the W. A. A. C.

(Col. Tasker stated that the policy of the W. A. A. C. would be to commission women physicians directly as officers in that service, since authority did not exist to commission women in the Medical Corps of the U. S. Army or to obtain a sufficient number of experienced women physicians on a contract surgeon basis.)

A general discussion of the role of educational methods in venereal disease prevention and in the prevention of pregnancy then ensued. In the course of this discussion it was brought out that medical officers specially qualified in these fields should be available to the W. A. A. C., and to this end it was recommended:

THAT A SPECIALLY TRAINED MEDICAL OFFICER BE PROVIDED TO HEADQUARTERS W. A. A. C. THROUGH THE DIVISION OF PREVENTIVE MEDICINE, OFFICE OF THE SURGEON GENERAL UNITED STATES ARMY, THIS OFFICER TO FUNCTION ADMINISTRATIVELY UNDER THE W. A. A. C., AND TO MAINTAIN THE SAME INFORMAL RELATIONSHIP WITH THE DIVISION OF PREVENTIVE MEDICINE, SURGEON GENERAL'S OFFICE, AS VENEREAL DISEASE CONTROL OFFICERS IN OTHER BRANCHES OF THE SERVICE. THIS OFFICER SHOULD DEAL WITH PROBLEMS OF SEX HYGIENE IN WOMEN AND RELATED PROBLEMS, INCLUDING VENEREAL DISEASE CONTROL.

It was requested at this point by Capt. Stephenson and Lieut. Col. Turner that a list of specially qualified women physicians, analogous to the list of men physicians trained in venereal disease control, previously prepared by the Subcommittee on Venereal Diseases, should be prepared by the Subcommittee and furnished to the Offices of the respective Surgeons General. Such a list is in process of formation, and will be forwarded when prepared.

There then ensued a general discussion of educational methods of disease prevention and contraception. Certain general principles were agreed upon:

1. It is unwise to assume that officers of the W. A. A. C. constitute a special group. They are as much in need of educational effort as enlisted personnel, and especially so because of the fact that they themselves will be called upon for educational effort with enlisted personnel under their command.
2. The problem should be regarded as primarily medical. Many forms of educational activity are required.
3. Women are more ready than is generally believed to accept instruction concerning these problems.
4. The strategy of educational effort should center largely on training centers, particularly those devoted to the training of officers. (In this connection it was brought out by Col. Tasker that the Des Moines training center is planned to accommodate a maximum of 7,000 women, and that the first group of 800 officer candidates is now enrolled. These candidates remain at Des Moines for from 4 to 10 weeks,

depending upon the type of training involved. Included in this training is a single lecture on hygiene, based on similar lectures given to Canadian women personnel, copies of which were not available to this Conference. It is planned that this lecture, covering a two-hour period, shall include such topics as the importance of group sanitation, feminine hygiene, the anatomy and physiology of sex, venereal disease, and pregnancy. It is further planned that this instructional material to officer candidates at Fort Des Moines will be given by women physicians, two of whom, names unknown, are now available as contract surgeons. The consensus of the Conference was that the amount of time to be devoted to these problems with officer candidates, as at present planned, is hopelessly inadequate, particularly in view of the desirability of the use of these potential officers in subsequent instruction of their own enlisted personnel.) It was further emphasized that, in the opinion of the Conference, immediate steps should be taken to augment the educational material available to these first groups of officer candidates.

5. Included in an educational program should be lectures, motion pictures, and pamphlets.

The conference took cognizance of the facts that:

a) Inexpertly performed educational effort on the part of medical or line officers is potentially productive of more harm among groups of women personnel than among groups of men.

b) The type of educational effort should differ in character, according to the type of personnel to which it is addressed, e.g., medical officers without special training in this field of public health, line officers, and enlisted personnel.

c) Educational effort requires modification from the type of material commonly offered college women as part of training for premarital and family relationships, in view of the fact that the aim of instruction of women in the Armed Forces is not primarily premarital, but instead disease-preventive and contraceptive.

d) Past experience with civilians indicates the need for caution in educational approach both as to contraception and prophylaxis, because of the inherent problem of public relations, and the possible political repercussions of public protest if mass instruction is too specific in nature. For this reason it was felt that mass educational effort, as by motion pictures and pamphlets, required particularly gentle and cautious handling; whereas oral instruction by properly trained medical officers, preferably women, might be much more frank and outspoken.

In view of these considerations and of the desirability of uniformity in methods of educational approach, this conference recommended that:

A SUBCOMMITTEE OF THIS CONFERENCE BE APPOINTED BY THE CHAIRMAN TO PREPARE FOR THE USE OF THE W. A. A. C. OUTLINES OF LECTURE AND PAMPHLET MATERIAL SUBDIVIDED ACCORDING TO THE PROBABLE USE TO WHICH IT MIGHT BE PUT, e.g., FOR SPECIALLY TRAINED MEDICAL OFFICERS, FOR MEDICAL OFFICERS IN GENERAL, FOR LINE OFFICERS, AND FOR ENLISTED

PERSONNEL.

Pursuant to this recommendation the Chairman appointed a subcommittee consisting of Drs. Mary Fisher, Chairman, Ernest Groves, Raymond Squier, Bertha Shafer, and E. L. Keyes, Tuxedo, N. Y. This subcommittee will meet in Washington on August 3rd and 4th, 1942, and will report promptly thereafter to the Chairman, Subcommittee on Venereal Diseases.

The problem of education by means of motion pictures was next discussed. It was brought out that there are no up to date films on sex hygiene for women. Certain films were made 20 or more years ago, which are now largely obsolete. It has been the experience of the American Social Hygiene Association that, so far as venereal disease is concerned, it is unnecessary to differentiate between the sexes in the context of films, and that those suitable for men are largely also applicable to women. No American films have so far been prepared which deal adequately with venereal disease prevention or with contraception. The Canadian Women's Army Auxiliary Corps has such a film in preparation, and the Russian Army has completed one which has been sent for and which will probably be available within a week at the Allied Council Repository.

AS TO PLANS OF THE ... it was said by Col. Tasker, speaking for the Army, that such a film was proposed. It was eliminated by order of the Director of Training SOS. Lieut. Mast, speaking for the Navy, said that a training film for women was being planned. Miss Zechiel presented the tentative outline of the proposed Navy film which includes details as to personal hygiene of a general nature, such as the care of the body, care of the feet, etc., the physiology of menstruation, the physiology of reproduction and of pregnancy, essential data as to contraception and venereal disease and venereal disease prophylaxis, and if possible some emphasis on minor psychiatric disorders which may be expected in women personnel from the altered conditions of group living, sex hazards, etc.

On the basis of this discussion it was agreed by the Conference and recommended that:

MOTION PICTURES ARE PARTICULARLY DESIRABLE IN THE EDUCATION OF W. A. A. C. PERSONNEL AS TO SEX HYGIENE AND THE RECOGNITION, TREATMENT, AND PREVENTION OF VENEREAL DISEASES. IF POSSIBLE, IN ORDER TO MINIMIZE EXPENSE AND TO ENSURE UNIFORMITY OF EDUCATIONAL CONTENT, ARMY AND NAVY SHOULD COLLABORATE IN THE PRODUCTION OF SUCH MOTION PICTURES TO BE UTILIZED BY THE W. A. A. C. AND BY THE ANALOGOUS WOMEN'S CORPS IN THE UNITED STATES NAVY, IF AND WHEN ESTABLISHED.

In this connection it was suggested that Miss Zechiel, a motion picture script writer attend the meeting with the group headed by Dr. Mary Fisher on educational technique.

At this point there ensued a long discussion as to the legal responsibility which might be incurred by the Armed Forces in the dissemination of contraceptive information and devices. After some discussion by members of the Conference, Mr. Morris Ernst, legal adviser of the Planned Parenthood Federation of America, spoke in effect as follows:

For a hundred years it was entirely lawful in the United States to advise and prescribe contraceptive methods and devices. In 1870 Anthony Comstock descended upon Congress with a Bill to make illegal the advertising of, the dissemination of information concerning, or the providing of contraceptives. This Bill was linked by Mr. Comstock with the dissemination of pornographic postal cards, copies of which he distributed freely among Congressmen. With five minutes debate in the House and no debate in the Senate, the Comstock Bill was passed. In the ensuing three years, 1870-1873, practically all the States followed the Federal Government in similar prohibitive statutes. An analysis of this legislation is available through Mr. Ernst on request. From 1870 to 1915 these prohibitive acts stood on the statute books without protest. In 1915, however, Margaret Sanger, a pioneer in the contraceptive field, brought about a test case in which she was convicted for dispensing contraceptive information. The case was appealed and in the Appeal Court the decision was reversed on the ground that such information was lawful if given in aid of health and the prevention of disease. The interpreting judge put a very broad interpretation on these words, which has been still further broadened by subsequent decisions in many other cases. Decisions are now on record in the highest courts of many States, and in the Federal Appeal Courts, indicating the legality of dissemination of contraceptive information or contraceptive devices. Only two states--Massachusetts and Connecticut--still hold out against this trend, and a pending case in Connecticut, which resulted in a split decision against contraception, has now been appealed to the Supreme Court of the United States. Up to this point the Supreme Court has, for various legal technicalities, refused to consider similar cases but it is hoped that the Connecticut case will result in a Federal decision which will be binding on all States. In Massachusetts, the only recalcitrant State, the question of legalizing contraceptive information and devices will be voted upon in a referendum at the general election in the fall of 1942.

Several States, among them North Carolina, have actually established birth control clinics operated by their State Health Departments. Mr. Ernst adds that there are, in various Federal Bureaus, legal opinions as to the complete legal immunity of the Federal Government to dispense monies to States for the purpose under Federal standards of providing contraceptive information and advice.

No case has arisen in the State or Federal Courts involving the sole issue of providing contraceptive advice or devices to unmarried women, but in many cases there are decisions which imply that no difference may be drawn because of marital status. In Mr. Ernst's opinion, on the basis of existing court decisions and existing legal opinions in various Government Bureaus, the Army may dispense contraceptive information and devices to unmarried as well as to married women; and such information may be given by means of motion pictures, pamphlets, or lectures. In Mr. Ernst's opinion the only risk involved is timidity and pussyfooting. Courage in presentation will, he believes, meet with public approval.

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As a result of this discussion by Mr. Ernst and of further discussion by members of the Conference it was agreed that both prophylactic and contraceptive advice should be made generally available to the personnel of the W. A. A. C. through the several educational techniques to be outlined by Dr. Fisher's sub-group.

In subsequent consideration of this opinion of the Conference, the Subcommittee on Venereal Disease specifically recommended that:

PERSONNEL OF THE W. A. A. C. SHOULD HAVE ACCESS TO CONTRACEPTIVE INFORMATION.

As to prophylaxis, it was pointed out that station prophylaxis of the type generally available to male personnel of the Armed Forces was not suitable for female personnel, partly because of lack of experience as to what constitutes adequate chemical prophylaxis in the female, and partly because of the improbability of use of such stations by women because of publicity. It was therefore agreed that major reliance, both in venereal disease prophylaxis and contraception, should be placed on mechanical prophylaxis, namely the condom; and that female personnel should be instructed in the proper use of this article. It was further agreed that condoms should be made as freely available to female personnel as to male personnel of the Armed Forces, and to this end the Conference specifically recommended that:

IN ORDER TO IMPLEMENT THE CONTROL OF VENEREAL DISEASE, AND IN RECOGNITION OF THE NECESSITY FOR PERSONAL AS OPPOSED TO STATION PROPHYLAXIS FOR THE FEMALE, CONDOMS SHOULD BE MADE AVAILABLE TO PERSONNEL OF THE W. A. A. C. UNDER CONDITIONS ENCOURAGING PRIVACY OF DISTRIBUTION.

It was felt that this might be better accomplished through slot machines, rather than by distribution or purchase through post exchanges; and that such slot machines might be inconspicuously located in women's quarters, preferably in toilets or wash rooms, and in a manner analogous to the dispensing of sanitary napkins. The provisions of this recommendation are obviously calculated to promote the use of mechanical prophylaxis when necessary by female personnel without undue publicity, either general or particular.

A discussion of chemical prophylaxis in females and the relationship of this to contraception ensued. No decision was reached as to any recommendation, since knowledge in the field of chemical prophylaxis in the female is inadequate. Dr. Squier, a conferee, volunteered to obtain and to furnish to the Chairman, Subcommittee on Venereal Diseases, through the National Committee on Maternal Health, such information as may be available on the prophylactic value of contraceptive jellies. Although no recommendations were made as to chemical prophylaxis, it was agreed by the conference that information concerning the use of contraceptive jellies for the purpose of contraception should be made available to the personnel of the W. A. A. C. by one or all of the educational techniques outlined above.

Further as to contraception, it was agreed that the diaphragm pessary was not an applicable device to personnel of the W. A. A. C. except in the case of married women living with their husbands.

* * * * *

There then ensued a discussion of certain collateral methods of venereal disease control. Questions were asked of Col. Tasker as to the disciplinary control of female personnel with regard to evening, over-night, and week-end leaves. Col. Tasker pointed out that at Fort Des Moines, which might be regarded as analogous to a military school, officer candidates were required to sign out as to the place of spending the evening, and were permitted to have over-night or week-end leave only on evidence of invitation by a family.

Whether such provisions would be generally applied later to enlisted personnel is not entirely clear. It was, however, pointed out that the duties to be expected of the W. A. A. C. were divided largely into two categories: (a) small groups of women attached to Army filter stations as airplane spotters, etc., etc., these women to be located primarily in large cities, and to live more or less as they might if they were civilians, perhaps even in their own homes; and (b) companies of women who might be sent to Army posts here or abroad to assume any duties which might release men for the fighting forces, these women living largely under barrack conditions. Disciplinary control of the two groups will of course differ.

After some discussion of this matter, the conference felt that efforts to impose "boarding school" types of discipline in adult female personnel of the W. A. A. C. might be extremely harmful to morale, and might actually promote, instead of prevent, sexual exposure. For these reasons the conference recommended that:

THERE SHOULD BE NO DISCIPLINARY DISCRIMINATION AS TO ABSENCE FROM QUARTERS, OVER NIGHT, WEEK END, OR OTHER LEAVE OR LIBERTY AS BETWEEN FEMALE W. A. A. C. PERSONNEL AND MALE PERSONNEL OF THE UNITED STATES ARMY.

Stress was laid on the desirability of ample recreational facilities for women, particularly on the basis of British experience. In this respect there was read to the Conference paragraphs 9 and 11 of the Sixth Report from the Select Committee on National Expenditure, Medical Services of the W. R. N. S., A. T. S., and W.A.A.F., April 1942. Questioned on this point, Col. Tasker reported that recreational facilities for the W. A. A. C. are planned to be more ample and more extensive than those available for male personnel of the U. S. Army. In this respect, therefore, no recommendations seemed to be called for.

As to case finding in venereal disease, Col. Tasker reported that a routine serologic test for syphilis was required on all officer candidates and enlisted personnel of the W. A. A. C., and that enrollment was being currently made on the basis of the March 15 edition of MR 1-9. He also reported that a routine pelvic examination will probably be made on all officer candidates, and on all enlisted personnel, married and unmarried. This latter procedure should exclude pregnancy, obvious cases of gonorrhoea, and serious gynecological disorders. In effect, therefore, the W. A. A. C. will occupy the same status as the U. S. Army, i.e., it will start with a non-venereally infected personnel insofar as this is possible.

There was then discussed the question of routine serologic testing of W. A. A. C. personnel on discharge from the service. It was agreed between Col. Turner and

Col. Tasker that the same procedure applicable to male personnel would be adopted if possible, and that circumstances permitting, such tests would be made routinely upon demobilization or discharge.

There next ensued a discussion of periodic medical examination as a method of case finding of venereal disease or pregnancy. It was pointed out (a) that the tendency in the Navy, if not in the Army, is to get away from such routine periodic examinations as degrading, both to enlisted personnel and to the officers who carry them out; and that in men their major usefulness seems to be as surprise examinations if concealment of disease is suspected and (b) that medical examination for venereal disease in women is technically a much more difficult matter than in men, requiring elaborate and costly laboratory examination, unlikely to be available. It was felt by the members of the conference that such periodic medical examinations in women presented insuperable difficulties, and it was therefore recommended that:

PERIODIC MEDICAL INSPECTION FOR VENEREAL DISEASE OR PREGNANCY BE NOT UTILIZED

IN THE W. A. A. C.

* * * * *

As to the treatment of venereally infected women, it was brought out on general discussion that plans for this have not as yet crystallized and that in any case the methods to be adopted will probably depend largely on local conditions. Nevertheless, stimulated by the reports of unfortunate experiences in Britain, the conference felt it desirable to adopt a recommendation that:

EVERY EFFORT BE MADE TO AVOID DISCRIMINATORY SEGREGATION OR STIGMATIZATION IN THE MANAGEMENT OF W. A. A. C. PERSONNEL WITH VENEREAL DISEASES; AND, WHERE POSSIBLE, WOMEN WITH THESE DISEASES SHOULD BE HANDLED IN THE SAME MANNER AS THOSE WITH OTHER ACUTE INFECTIOUS DISEASES.

* * * * *

The question was raised as to the disposition of pregnant women. Tentative regulations of the W. A. A. C. provide for the honorable discharge of a married woman who becomes pregnant, with the proviso that she may re-enroll at an appropriate date after delivery. In the case of an unmarried woman, however, regulations provide that if such a woman becomes pregnant she shall be given a summary discharge (according to Col. Tasker, this is equivalent to "discharge without honor") and that she may not subsequently re-enroll. The question was further raised as to the distinction in the lay mind between "summary discharge" or "discharge without honor" and "dishonorable discharge", and the Conference agreed that the distinction, if any, was nebulous. It was pointed out by several members that such a "discharge without honor" might redound to the ultimate serious detriment of the woman in question in her subsequent career in civil life, and might unjustly stigmatize her. It was further brought out, not altogether facetiously, that if a married woman of the W. A. A. C. became pregnant by some other man than her husband, there would exist some doubt as to the category of her discharge whether "honorable" or "without honor".

Because of the serious social implications of this ruling the conference felt it desirable to put itself on record with a recommendation that:

PREGNANCY SHOULD NOT BE A GROUND FOR SUMMARY DISCHARGE FROM THE W. A. A. C.
A PREGNANT WOMAN SHOULD BE DISCHARGED ON THE GROUND OF PHYSICAL DISABILITY WITHOUT PREJUDICE TO SUBSEQUENT ENROLLMENT.

It was emphasized that this provision followed British experience, made no distinction between married and unmarried women, and had no bearing on legitimacy or illegitimacy of the child.

In further discussion of the question of pregnancy in the W. A. A. C. it was pointed out that the environmental change to which women from civilian life would suddenly be subjected would bring about many menstrual irregularities and periods of prolonged amenorrhea; and that these menstrual irregularities, with or without the possibility of actual pregnancy, might contribute to various psychiatric disorders in feminine personnel unless steps for the early recognition of pregnancy are available. For this reason the Conference recommended that:

THE MEDICAL CORPS UNITED STATES ARMY BE PREPARED TO PERFORM A LABORATORY TEST FOR PREGNANCY ON FEMININE PERSONNEL WHEN INDICATED.

Finally, when this report and its recommendations were subsequently presented to and approved by the Subcommittee on Venereal Diseases (on July 24, 1942), the Subcommittee rediscussed the entire question of punitive measures for the acquisition of venereal diseases as applied to the W. A. A. C. These include the designation of venereal disease as "due to misconduct", and consequent loss of pay for loss of time. Although previous recommendations of the subcommittee for the abolition of all punitive measures for venereal diseases in male personnel of the Armed Forces have not been accepted, it was felt that the auxiliary status of the W. A. A. C., which serves with but not in the Army, offers an opportunity to reiterate the generally accepted public health principle, i.e., that punishment for venereal disease promotes the concealment and fosters the spread of these diseases. It was therefore specifically recommended that:

SINCE THE SUBCOMMITTEE ON VENEREAL DISEASES HAS ALREADY GONE ON RECORD AS ADVISING THE DISCONTINUANCE OF ALL FORMS OF PUNITIVE REGULATIONS, INCLUDING LOSS OF PAY FOR LOSS OF TIME, ATTACHED TO THE ACQUIRING OF VENEREAL DISEASE IN THE U. S. ARMY AND NAVY; AND SINCE THE SUBCOMMITTEE FEELS THAT PUNITIVE REGULATIONS ATTACHING TO THE ACQUIRING OF VENEREAL DISEASE IN WOMEN PRESENT EVEN MORE UNMANAGEABLE PROBLEMS, CONCERNED WITH THE TRANSMISSION, CONCEALMENT, AND DIAGNOSIS OF THESE DISEASES THAN IN MEN, NO ATTEMPT WHATEVER BE MADE TO EMPLOY ANY FORM OF PUNITIVE REGULATION

IN DEALING WITH VENEREAL DISEASE IN THE W. A. A. C. OR OTHER AUXILIARY FEMALE
PERSONNEL.

At 4:00 P.M. the meeting adjourned.

Respectfully submitted,

J. E. Moore, M.D., Chairman.

AGENDA
To Meeting of Subcommittee on Venereal Diseases
National Research Council
May 27, 1942

I. Consideration of the revision of the gonorrhoea memorandum - Circular Letter No. 18.

(This memorandum has now been agreed to by all members of the committee except Dr. Cox who takes exception to paragraph E 2d, page 4; and a suggested revision by Dr. Clarke of paragraph B 1, page 1.)

II. Report of conference on chemical prophylaxis of venereal disease, together with report of the Chairman on subsequent information gathered from other sources.

A. The Production of Gonococcal Infection in Experimental Animals.

Inquiry has been made to a number of bacteriologists concerning the possibility of the production of experimental gonococcal infection. Dr. K. Sternbach of the University of Toronto has apparently succeeded in producing conjunctival infection in rabbits previously poisoned with benzine. These experiments are incomplete.

Research applications in the general field of the chemical prophylaxis of gonorrhoea have been received from:-

Dr. Justine Hill, Johns Hopkins University
Dr. C. Phillip Miller, University of Chicago
Dr. Frederick B. Bang, Rockefeller Institute for Medical Research
(See below)

B. The Local Use of Sulfathiazole Ointments in the Human Urethra.

Studies in this direction have been undertaken by Dr. Murray Sanders, Columbia University, who is proceeding without proposal for OSRD contract.

Dr. Alfred Cohn, New York City Department of Health, has undertaken local treatment of patients with acute gonorrhoea.

Dr. E. K. Marshall has raised the issue that the local use of sulfonamides may be without effect.

C. The Chemical Prophylaxis of Chancroid.

This problem has been undertaken by Dr. Frank C. Combes whose proposal for contract is listed below.

It is also under consideration by Drs. Sanderson and Greenblatt, University of Georgia.

D. Prophylaxis of Lymphogranuloma Venereum.

Studies in this field are being undertaken by Dr. Murray Sanders. No OGRD contract is involved; and by Dr. Geoffrey Rake. See his proposal for contract listed below.

E. Prophylaxis of Granuloma Inguinale.

Information has been received as to the probable spontaneous occurrence of this disease in dogs. Drs. Sanderson and Greenblatt may attempt the experimental production of the disease in these animals.

F. Prophylaxis of Syphilis.

A study has been undertaken to evaluate the efficacy of calomel ointment. This has been begun jointly in the laboratories of Drs. Eagle, Chesney, and Turner at the Johns Hopkins University, and is covered in part in a proposal for contract submitted by Dr. Eagle. (See below).

III. Report of the Chairman on a Conference on Biologic False Positive Serologic Tests for Syphilis.

This conference has led to three research proposals - from Dr. Herbert Lund, Drs. Wellman, Kline and Lankelma, and Dr. R. L. Kahn. These are listed below.

It was suggested at the conference on March 26 that a further conference be called of chemists interested in the possible elucidation of this problem. Correspondence has been held with a large number of potentially interested chemists and physicists with inconclusive results, summarized in a memorandum from Dr. Eagle. The recommendations of the committee are desired with regard to such a conference.

IV. Consideration of the following Proposals for Contract.

A. Justina H. Hill, Johns Hopkins University, "The Establishment of Gonococcal Infection in Experimental Animals by Methods Applicable to the Study of Venereal Disease."

B. C. Phillip Miller, University of Chicago, "Prophylaxis of experimental gonococcal infection; more specifically an attempt to produce in some laboratory animal gonococcal infection in a mucous membrane suitable for the testing of prophylactics."

C. Frederick B. Bang, Rockefeller Institute for Medical Research, Princeton, N.J. "Chemical prophylaxis of gonorrhoea."

D. Charles M. Carpenter, University of Rochester, -

E. Frank C. Combes, New York University and Bellevue Hospital, "Pro-

phylaxis of Chancroid."

F. Geoffrey Rake, Squibb Institute for Medical Research, New Brunswick, New Jersey:-

1. "Prophylaxis against lymphogranuloma venereum"
2. "Development of a prophylactic agent effective against all venereal diseases."

G. Harry Eagle, Johns Hopkins University and the U. S. Public Health Service. "Studies in the treatment and prophylaxis of syphilis."

(This proposal is divided into 3 parts: (1) a study of the effect of soap and calozel ointment in the prophylaxis of syphilis; (2) a study bearing on the toxicity of arsenical drugs. - This study is of major interest to the Committee on the Treatment of Gas Casualties, the Chairman of which Dr. M. C. Winternitz, has informally expressed a desire for prompt prosecution of this phase of Dr. Eagle's work. (3) A study of spirochetal complement fixation tests, a subject of potential value in the elucidation of biologic false positive serologic tests.

H. Sanderson and Greenblatt, University of Georgia " -

I. Herbert Lund, Western Reserve University. "The nature of biologic false positive reactions in the serology of syphilis."

J. Drs. Wellman, Kline, and Lakelma, Western Reserve University and Mt. Sinai Hospital. "To isolate the most potent and most specific fraction of tissue extracts (beef heart powder) for use in serodiagnostic tests for syphilis."

K. Reuben L. Kahn, University of Michigan, "Studies on the verification test (Kahn) in the detection of false positives in the serodiagnosis of syphilis."

V. Possible revision of a system of treatment of syphilis, at the suggestion of the U. S. Army.

~~RESTRICTED~~

MINUTES OF THE FIFTEENTH MEETING OF THE
SUBCOMMITTEE ON VENEREAL DISEASES - NATIONAL RESEARCH COUNCIL

May 27, 1942.

The fifteenth meeting of the Subcommittee on Venereal Diseases, National Research Council, was held in Washington on Wednesday, May 27th. Present were:

Dr. J. E. Moore, Chairman, Drs. Stokes, Cox, Herrold, Clarke, Mahoney, and Nelson, members of the Subcommittee;
Drs. Weed, Cushing, Larkey, and Forbes, Division of Medical Sciences, National Research Council;
Dr. Perrin Long, Committee on Chemotherapeutics and Other Agents;
Dr. E. C. Andrus, Committee on Medical Research;
and the following liaison officers from the U. S. Army, Navy, and Public Health Service:-

Cols. Hugh Morgan and George Callender, Lieut. Col. Prontiss and Lt. Col. T. B. Turner, Major W. A. Brumfield, Captain C. S. Stephenson, and Dr. R. A. Vonderlehr.

The Chairman announced that at the request of Colonel Hugh Morgan, Division of Professional Services, and Lieut. Col. T. B. Turner, Subdivision of Venereal Diseases, Surgeon General's Office, a preliminary meeting had been held in Washington on May 26th, attended by Cols. Morgan and Turner, Major Brumfield, and Capt. Shull of the U. S. Army, Dr. Harry Eagle of the U. S. Public Health Service, and Dr. John H. Stokes of the Subcommittee on Venereal Diseases. This meeting was called by Cols. Morgan and Turner at the suggestion of the Surgeon General with the thought in mind that the system of treatment for syphilis previously recommended by the Subcommittee on Venereal Diseases might possibly be modified and shortened. The treatment system previously recommended is proving unduly cumbersome and time consuming under field conditions and is therefore difficult to carry out. The prolonged duration of treatment required by that system may be a factor which has heretofore prevented the acceptance by the U. S. Army of syphilitic registrants. A modification of this treatment system which materially shortens its duration would be of value to the Armed Forces in the conservation of man-power and might possibly open the door to acceptance by the Army of syphilitic registrants still in need of some antisiphilitic treatment.

The Chairman then explained that because of recent advances in syphilotherapy, both from the clinical and laboratory standpoints, stimulated by studies on the intensive arsenotherapy of early syphilis, it seemed possible to the persons present at the preliminary meeting on May 26th to evolve a satisfactory compromise between the C. C. G. system of 15 to 18 months' continuous antisiphilitic treatment and the intensive arsenical courses experimentally utilized up to this point. The consensus of this meeting was that 85 per cent of all these with early syphilis could be "cured" by a six months' treatment system comprising 40 intravenous injections of mapharsen to an approximate total dosage of 2400 milligrams, and 16 intramuscular injections of bismuth; and that these results would certainly be as satisfactory in early syphilis as the prolonged treatment system now in vogue.

It was also the consensus of the preliminary meeting that similarly adequate results could be obtained with this six months' treatment system in patients with latent syphilis. At the preliminary meeting therefore a recommendation for a new system of treatment of syphilis was drawn up.

This recommendation, ~~is~~ herewith appended as "Exhibit A", was presented to the Subcommittee on Venereal Diseases, and passed.

There was next considered a new memorandum covering treatment of gonorrhea designed to replace Circular Letter No. 18, which embodies the previous recommendations of the Subcommittee on Venereal Diseases. This new memorandum was elaborated by a sub-group consisting of Drs. P. S. Pelouse, Russell Herrold, Rogers Deakin, and Oscar Cox. After considerable further discussion by the Subcommittee on Venereal Diseases, both by mail and in the course of the current meeting, this memorandum was likewise approved as a recommendation and is herewith appended as "Exhibit B."

The Chairman then reported on the conference on biologic false positive serologic tests for syphilis and on the chemical prophylaxis of venereal diseases held under the auspices of the Subcommittee, respectively, on March 26th and March 11th, 1942. The Minutes of these conferences have already been circulated.

As to biologic false positive serologic tests, the Chairman reported on the recommendations of that conference as follows:--

(1) The recommendation of the conference was that proposal for contract by Dr. Reuben L. Kahn be further considered by the Subcommittee. This was done later in the meeting and the action taken will be found later in these Minutes.

(2) The conference recommended that further work continue with spirochetal complement fixation tests in the laboratory of Dr. Harry Eagle and of Dr. John A. Kolmer. The Chairman reports that nothing further has been heard from Dr. Kolmer in this respect, but that further such work in Dr. Eagle's laboratory is covered in a proposal for O.S.R.D. contract considered later in this meeting, the action on which will be found later in the Minutes.

(3) The Conference recommended that the Lund technique should be further studied. The Chairman reports that this has resulted in a proposal for contract by Dr. Lund, considered and acted upon later in this meeting (see below).

(4) The Conference recommended that a further conference be called of chemists working in the field of the serology of syphilis, to determine what, if any, further studies were desirable in the identification of the reacting substance in tissue extract antigens or of the chemical nature of reagin. The Chairman reported that this recommendation had resulted in a proposal for contract from Drs. Kline, Wellman, and Lankelma of Western Reserve University, considered later in the current meeting, action on which is reported below.

As to the proposed additional conference, the Chairman reported that he

had written the following letter to a number of scientists in the country.

"Dear Doctor:-

The Subcommittee on Venereal Diseases, National Research Council, is much concerned with various problems in the serologic diagnosis of syphilis. Of these the one of outstanding importance at the present moment is the question of biologic false positive serologic tests in normal persons, or in nonsyphilitic persons suffering from diseases other than syphilis. There is a large literature in this field which may be briefly summarized as follows:-

A) Many normal animal species react positively in varying proportions, ranging from 1 or 2 per cent to as high as 95 per cent, with standard serologic tests for syphilis, either flocculation or complement fixation, or both. In some of these animal species, i.e., cows, the content of reagin or reagin-like substance in the blood is relatively high.

B) There is evidence that reagin or a reagin-like factor may exist in low concentration in the blood of many normal human beings and that in some of them, either temporarily or permanently, the quantity of this substance in the blood may be sufficient to produce false positive serologic tests for syphilis in nonsyphilitic persons.

C) There is likewise evidence that in a number of diseases other than syphilis, e.g., malaria, infectious mononucleosis, acute upper respiratory infections, etc., there appears in the blood of nonsyphilitic persons reagin, or a reagin-like substance, which temporarily during the acute phase of nonsyphilitic illnesses may produce weakly or strongly positive serologic tests for syphilis.

D) The standard serologic tests for syphilis depend on the use of tissue extract antigens. These antigens consist of alcoholic extracts of mammalian tissue, usually beef heart, fortified with sterols, and contain many different substances. It is probable that the substance in these antigens responsible for their reactivity with the serum of syphilitic persons has not as yet been accurately identified.

E) Nothing is known as to the physico-chemical nature of reagin except that it is associated with the globulin fraction of serum, and it is not known whether the reagin-like substance in the blood of normal animals, or normal persons, or of persons suffering from diseases other than syphilis, differs quantitatively or qualitatively from the reagin produced during syphilitic infection.

The serologic diagnosis of syphilis and the differentiation of the biologic false positive serologic tests from those actually due to syphilitic infection would be enhanced if (a) the reactive factor in tissue extract antigens could be chemically identified; and (b) if the chemical nature of syphilitic reagin and its possible qualitative difference from the reagin-like factor accounting for biologic false positive tests could be established.

" The serologists of the country are for the most part without experience in physical chemistry. It has been suggested by a number of preliminary conferences that a solution of the problems enumerated above and with others dealing with the serologic diagnosis of syphilis, might be enhanced by a conference of physicists, physical chemists, and lipid chemists.

Your name has been suggested as one of the outstanding physicists or physical chemists interested in the field of the application of optical properties to chemical problems. It is requested that you write me your opinion as to whether anything would be gained by such a conference, including among its personnel a clinician, a serologist, and one or several of the persons enumerated at the bottom of this letter.

Sincerely yours,

S/ J. E. Moore, M.D., Chairman,
Subcommittee on Venereal Diseases. "

These scientists included the following lipid chemists :- Dr. Erwin Chargaff, Department of Biochemistry, Columbia University, New York; Dr. H. M. Sinclair, Queens Medical School, Kingston, Ontario; Dr. W. K. Sperry, New York Psychiatric Institute, New York; Dr. C. Artun, Wake Forest Medical School, Wake Forest, N.C.; and the following physicists, after the name of each of whom appears the special technique employed by him, concerning which these scientists were requested to express an opinion as to the availability of this technique in such a study:

- Dr. W. R. Brode, Visible and Ultraviolet Spectroscopic Analysis, Ohio State University, Columbus, Ohio.
- Dr. E. Bright Wilson, Infrared Spectrophotography, Harvard University, Cambridge, Mass.
- Mr. M. L. Huggins, X-ray Diffraction, Eastman Kodak Company, Rochester, New York.
- Mr. C. L. Davison, Electron Diffraction, Bell Telephone Laboratory, 195 Broadway, New York.
- Dr. L. Marton, The Electron Microscope, Stanford University, San Francisco, California.
- Dr. W. Bleakney, The Masked Spectrograph, Princeton University, Princeton, N.J.

The answers received from these several scientists were reviewed by the Chairman, and at his request by Dr. Harry Eagle; and are summarized in a memorandum from Dr. Eagle, which follows herewith:-

"In accordance with your request, I have been over the correspondence relating to a proposed conference for chemists, physicists, and others, with a view to the possible purification and chemical identification of antigen, and perhaps of syphilis reagin. After going over those letters, it seems to me that such a conference would be premature at the present time, and that some preliminary laboratory study is indicated which may either emphasize the necessity for a conference, or render it inadvisable.

Your committee is, I believe, interested in the purification of tissue antigens primarily because it is disturbed by the large number of normal persons who give what are apparently biologic false positive tests for syphilis with crude tissue extracts. The entire problem thus hinges on the answers to just two questions: 1) can the active material in those crude extracts be isolated; and (2) if so, does the pure material have the same undesirable reactivity with normal animal serum, normal human serum, and with sera giving biologic false reactions, as do the crude tissue extracts; or, is the purified material more specific? As is indicated in the letters of some of the chemists you have consulted, the first laboratory approach would appear to be a critical examination of the "cardiolipin" isolated by Doctor Pangborn from beef heart tissue, and which she believes to be the specifically active substance in tissue extracts. Careful quantitative studies on the relative activity of crude extracts and of these purified materials are, however, necessary, in order to demonstrate that this purified lipid is actually the reactive material, rather than an inert substance carrying with it a small amount of the active material as an impurity. Such data do not appear in the papers published to date from Doctor Pangborn's laboratory. Rather than have some chemist working under the auspices of your committee repeat the laborious procedures for the purification of "cardiolipin" and lecithin, as described by Doctor Pangborn and Doctor Maltaner, it would probably be simpler to have some of Doctor Pangborn's materials assayed for activity in her own and also in some outside laboratory.

The further course of the study, and specifically the advisability of a conference, would be determined by the outcome of this preliminary study. a) If Doctor Pangborn's cardiolipin is the long-sought reactive factor, the problem is the straightforward one of determining its specificity as compared with that of crude extracts. If it gives just as many false reactions, we can forget about the purification of tissue extracts as an answer to the problem of specificity. b) However, if "cardiolipin" proves to be no more active than crude extracts per unit solid, and is therefore not the reactive material, then a conference aimed at ways and means of isolating that substance might be profitable - and the letters you have received contain some valuable suggestions as to lines of attack.

The other main problem which has been suggested is the identification and isolation of syphilis reagin, and its differentiation from normal reagin or from that elaborated in other diseases. Reagin is known to be a globulin; in view of its minute concentration, and in view further of the fact that most antibodies cannot be chemically differentiated even from normal serum globulin, attempts to differentiate chemically between different kinds of reagin would seem to be not too promising. On the other hand, it would be worth while to identify, by electrophoretic studies, the fraction of globulin (alpha, beta or gamma) with which syphilis reagin is associated, and then to identify the fraction of the serum protein which carries the "normal" reagin, or that factor responsible for biologic false positive diagnostic tests. Such a study would entail the collaboration of a physical chemist working with a large-scale Tiselius apparatus suitable for the fractionation of serum protein, and an immunochemist familiar with both protein chemistry and serology, to study the serologic reactivity of the several protein fractions."

This led to further discussion by the Subcommittee which resulted in two actions:

1) The Chairman was authorized to write to Dr. Mary C. Pangborn to enquire whether her laboratory was prepared to produce "cardiolipin" on a sufficiently large scale to permit further study of it in her own laboratory and to supply one or more other laboratories with this substance for similar studies.

2) The Chairman was also authorized to write to Dr. Edmund Cohn, Harvard University, Dr. William Welker, University of Illinois Medical School, and to Dr. Elvin Kabat in Dr. Heidelberger's laboratory at Columbia University, these three being physical and immunochemists who are believed to have available methods of study which might be of aid in the further identification of reagin.

As to the Conference on chemical prophylaxis of venereal disease, held on March 11th, the Chairman reported as follows:-

1) This Conference recommended that certain experiments concerning the prophylactic activity of soap and of calomel ointment be undertaken in the laboratories of Drs. Harry Eagle, A. M. Chesney, and T. B. Turner, the Johns Hopkins Hospital. The Chairman reports that these studies have already been begun and are covered in a proposal for O.S.R.D. contract by Dr. Harry Eagle, action concerning which will be found later in these Minutes.

2) The Conference recommended that experiments looking toward the production of gonococcal infection in experimental animals be undertaken in the laboratories of Dr. Justina Hill, Johns Hopkins University and Hospital, and perhaps in others. The Chairman reports that this recommendation has resulted in a proposal for O.S.R.D. contract from Dr. Hill and from Dr. Phillip Miller, University of Chicago, action on which appears later in these Minutes.

3) The Conference further recommended that Dr. Donald Pillsbury summarize existing knowledge as to skin penetrants. The Chairman reports that Dr. Pillsbury has submitted such a memorandum which was appended as "Exhibit B" to the Minutes of the Conference.

4) The Conference further authorized the Chairman to approach certain other investigators with regard to the chemical prophylaxis of venereal diseases. Concerning this the Chairman reports that interviews were later held with Dr. Murray Sanders, Columbia University, Dr. Geoffrey Rake, Squibb Institute, and Dr. F. B. Bang, Rockefeller Institute, Princeton, N.J.; and that the Chairman has corresponded with various others, including Dr. Alfred Cohn of New York and Drs. Sandersen and Greenblatt of the University of Georgia.

As to Dr. Sanders, the Chairman read the following memorandum submitted by him:

"MEMORANDUM ON VENEREAL CHEMO-PROPHYLAXIS

"The problem of prophylaxis of certain venereal diseases has been approached by local application of sulfonamide-containing ointments. We are attempting to answer four general questions:-

First, can a practicable and convenient prophylaxis against sulfonamide susceptible diseases (gonorrhea, lymphogranuloma venereum, and chancroid) be obtained?

Second, do such ointments produce local irritation?

Third, does absorption of the sulfonamides into the blood stream occur from the local site of administration?

(It should be noted that the only purpose in studying sulfonamide blood levels is to demonstrate passage of the drug from mucous membrane surface across the tissue barrier into blood - not to obtain therapeutic levels.)

Fourth, how long do the ointments persist on the mucous membrane surface?

The following studies have been carried out. Normal individuals have received, intraurethraly, various types of sulfonamide ointments. The ointments have been prepared by the Warner Institute for Therapeutic Research, New York. It should be emphasized that, although a total of 65 normal individuals have received 5 different ointments, at no time has there been the slightest indication of local irritation or systemic reaction.

At the suggestion of Dr. Moore, particular emphasis was placed upon a 'foamy' type of ointment which would act like a soap (without the addition of water) when applied locally, and would also have the properties of a vanishing cream. Such an ointment was compounded by the Warner Company and has been tested on 40 normals and 14 patients known to be infected with gonorrhea. It is easily applied, is non-irritating (so far), and leaves practically no greasy residue.

In preliminary tests with this ointment in the infected patients, Dr. Alfred Cohn has ventured the opinion that clinical and bacteriologic improvement has followed its intraurethral application. There has also been a suggestion that a small amount of this ointment may be expressed from the urethra 24 hours after administration. Although too few blood levels have been done to make a definite statement as to the passage of the drug into the blood stream, it is certain that some absorption does take place.

Appreciating the fact that all these data are too scanty to evaluate, it seems desirable to have the following questions answered at this time before the various members of the group continue with the plan outlined above:-

1. Is it desirable to continue the study of chemo-prophylaxis of venereal disease by local application?

2. Would it be feasible to test such an ointment in the field if a rather large number of normal individuals (about 100) were to show no ill effects after multiple applications of the ointment intraurethrally?

A portion of these patients could be studied carefully for drug absorption, i.e., blood level determinations carried out one half hour, an hour and a half, 3, 5, and 7 hours after instillation of the ointment.

An attempt will also be made to study hospitalized gonorrhoeal patients."

This memorandum indicates that Dr. Sanders has already begun certain experiments looking toward the use of sulfonamide ointments in the urethra, and that these ointments have been used both in normal persons by himself, and in persons with acute gonorrhoeal urethritis by Dr. Cohn. A general discussion of Dr. Sanders' work was held and the Chairman was authorized to correspond further with Dr. Sanders with the request that his work be continued and expanded. It was suggested that he should be asked to employ micro crystals of sulfonamide preparations, since those which he is using contain crystals from 3 to 100 micra in length; and that such crystals might do organic damage to the urethra. Micro crystals, 1 to 3 micra in length, would avoid such damage and would provide better interface reactions. It was brought out that such crystals are available only from Smith, Kline, and French; but it was felt that these preparations might be made available to Dr. Sanders through the intermediation of Dr. Ferrin Long.

It was further suggested that from the technical point of view, micro crystals of sulfanilamide should also be tried because of the superior local effect of this sulfonamide compound on other micro organisms. The preparation should probably be utilized at an approximate pH of 7.4.

The Chairman brought out the fact that Dr. Sanders might be unable to expand this work because of his entry in the near future into the Armed Forces; but the Subcommittee felt the work to be of such value that it should be continued either by Dr. Alfred Cohn or by Dr. Sanders' associate, Dr. Fox.

The Chairman next reported that his interview with Dr. Rake had resulted in a proposal for contract by Dr. Rake, action on which is reported later in these Minutes.

Likewise the Chairman reported that correspondence with Dr. Frank Combes has resulted in a proposal for contract, action on which is detailed later in these Minutes.

The Chairman further reported correspondence with Drs. Sanderson and Greenblatt has resulted in certain experiments by them, detailed in a letter from them, dated April 8, herewith reproduced:-

"Referring to your letter of March 29, I believe we here could plan experiments as follows:-

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1. Chancroid. a) Auto-inoculation of chancroid patients in several areas, testing chemical prophylaxis of soap, sulfathiazole ointment, etc.

b) Similar testing on volunteers with negative dermal reactions, using pure culture as infecting agent.

c) We have not been able to infect small animals with *H. Ducreyi*, although it was not tried on the genitalia.

2. Lymphogranuloma Venereum. Auto-inoculation of patients with unilateral lube, testing chemicals as above. It is questionable whether we could risk the inoculation of non-infected individuals, as curative procedures are dubious.

3. Granuloma Inguinale. a) Auto-inoculation can be done using test chemicals for prophylaxis. In nearly all cases we would be dealing with a mixed infection, and data would have to be interpreted accordingly.

b) Inoculation of volunteers with mixed material. Interpretation as above.

c) Inoculation of volunteers with material containing only Donovan bodies, and testing of chemical agents. In our experience the sources of such material are so rare, that it would be a long time before informative data could be expected. Goodpasture et al, using material not altogether unmixed, were able to infect monkeys. The lesions were not progressive and healed spontaneously. Based on his work, would not think the monkey altogether satisfactory for prophylactic experiments. With limited amount of 'pure' material, we here have not been able to produce lesions in smaller animals as yet. Chick membranes failed also.

We are carrying on other lines of approach, but perhaps the above is more in keeping with what you desire at present.

Sincerely yours,

S/ E. E. Sanderson
Robert Greenblatt."

Drs. Sanderson and Greenblatt write further, on May 25, to say that these problems can be carried on for the time being with funds already allocated but that supplementary funds may be requested at a future date.

The Subcommittee then proceeded to a consideration of the following proposals for O.S.R.D. contract:

A. Justine H. Hill, Johns Hopkins University, "The Establishment of Gonococcal Infection in Experimental Animals by Methods Applicable to the Study of Venereal Disease," in the amount of \$5,000. This was accepted and rated A.

B. C. Phillip Miller, University of Chicago, "Prophylaxis of experimental gonococcal infection; more specifically an attempt to produce in some labora-

tery animal gonococcal infection in a mucous membrane suitable for the testing of prophylactics," in the amount of \$5,800. It was felt by the Subcommittee that as Dr. Miller's application was phrased, it involved only the repetition of work which had already been done by him unsuccessfully. Action on his proposal was therefore postponed, pending conference with him by Dr. Russell Herrold, a member of the committee, who was instructed to write to the Chairman after such a conference with his opinion as to the probability that Dr. Miller had any new approach to the problem.

G. Frederick B. Bang, Rockefeller Institute for Medical Research, Princeton, N.J. "Chemical prophylaxis of gonorrhea," in the amount of \$3,150. This proposal which involves the use of chick embryos infected with gonorrhea, was accepted and rated A.

D. Charles M. Carpenter, University of Rochester, "The development and testing of chemical prophylactics for the treatment of venereal disease," in the amount of \$10,800. This proposal resulted in considerable discussion which ended in authorization to the Chairman to return Dr. Carpenter's proposal to him with the request for further information. This has been done in the following letter:-

May 29, 1942.

"Dear Doctor Carpenter:-

Your proposal for contract for the development and testing of chemical prophylactics for the treatment of venereal disease was discussed in detail at a meeting of the Subcommittee on Venereal Diseases held in Washington on May 27th. Three comments were made:

First, that the formulae suggested in your plan of attack contained a great many ingredients and that you might be hard put to it if a given formula worked, to decide which ingredient was doing the trick. It was thought that if one such formula should prove to be effective, you might then be under the obligation of breaking this down item by item to provide information as to the effective substance. The suggestion was made that perhaps it would be simpler to start with individual ingredients and to build up formulae on something other than an empirical shot-gun basis.

Comment was also made on the fact that certain of the ingredients in your formulae were obviously proprietary substances, the nature of which is presumably unknown to you and certainly unknown to us.

Finally, in this same connection, no one of the persons present at the meeting, some of whom are familiar with emulsion bases, wetting agents, etc., had any knowledge of what was represented by "colloidal phase".

Second, it was felt that the proposed in vitro exclusion tests would be valueless so far as gonorrhea is concerned and unnecessary as to syphilis. As to gonorrhea, the members of the Subcommittee are convinced that the only feasible methods of demonstrating the prophylactic activity of any chemical substance depend first on the production of experimental gonococcal infections in

animals (which has not yet been accomplished); or by the demonstrable therapeutic effect of such substances used locally in patients with fresh gonococcal anterior urethritis. As to syphilis, it is agreed that in vivo tests are so much more satisfactory than in vitro tests as to make it undesirable to waste time on the latter.

The amount of money requested seemed to the Subcommittee to be relatively large and the questions were raised as to the manner in which you propose to employ the two thirds' time of a chemist and the full time of a bacteriologist.

Finally, the opinion was expressed that, in view of your previous O.S. R.D. contract with Warren for the investigation of the combined effects of fever and chemotherapy in experimental animals, and in view of the public health activities in Glyn County, Ga., you might be putting yourself in the position of biting off more than you can chew.

The Subcommittee has therefore authorized me to return your application to you and has postponed action on it, pending clarification of these several points. Would you be good enough to go over it in detail in the light of this letter, and to return it to me at your earliest convenience.

Sincerely yours,

S/ J. E. Moore, M.D., Chairman
Subcommittee on Venereal Diseases."

E. Frank C. Combes, New York University and Bellevue Hospital, "Prophylaxis of Chancroid," in the amount of \$100. This proposal was accepted and rated A, but it was felt that the amount requested should be treated as supplementary to his already existing O.S.R.D. contract.

F. Geoffrey Rake, Squibb Institute for Medical Research, New Brunswick, New Jersey: (1) "Prophylaxis against lymphogranuloma venereum", (2) "Development of a prophylactic agent effective against all venereal diseases. No funds requested. This proposal, which is a token contract only, involving no request for funds, was accepted and rated A.

G. Harry Eagle, Johns Hopkins University and the U. S. Public Health Service. "Studies in the treatment and prophylaxis of syphilis, in the amount of \$4,000. This proposal was accepted and rated A. ←

H. Herbert Lund, Western Reserve University, "The nature of biologic false positive reactions in the serology of syphilis," in the amount of \$4,895. This proposal was accepted and rated A. ←

I. Drs. Wellman, Kline, and Lankelma, Western Reserve University and Mount Sinai Hospital, Cleveland, "To isolate the most potent and most specific fraction of tissue extracts (beef heart powder) for use in serodiagnostic tests for syphilis," in the amount of \$2,400. This proposal was accepted and rated A.

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→ J. Reuben L. Kahn, University of Michigan, "Studies on the verification test (Kahn) in the detection of false positives in the serodiagnosis of syphilis," in the amount of \$12,450. This proposal was rejected on the grounds embodied in a letter subsequently written to Dr. Kahn which follows:-

May 30, 1942.

Dr. Reuben L. Kahn
University Hospital
Ann Arbor, Mich.

Dear Doctor Kahn:

At a meeting of the Subcommittee on Venereal Diseases, National Research Council held in Washington on May 27th, there was considered your proposal for contract on "Studies of the Verification Test (Kahn) in the Detection of False Positives in the Serodiagnosis of Syphilis." It was decided to reject this application on the grounds that it is not yet established whether the "verification test" is a biological or a technical phenomenon, and that its usefulness in a study of false positive serologic tests has not yet been established.

Very truly yours,

S/ J. E. Moore, M.D., Chairman,
Subcommittee on Venereal Diseases."

The meeting then adjourned.

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MINUTES OF THE FOURTEENTH MEETING OF THE

SUBCOMMITTEE ON VENEREAL DISEASES- NATIONAL RESEARCH COUNCIL

March 11, 1942

The fourteenth meeting of the Subcommittee on Venereal Diseases, National Research Council, was held in Washington on Wednesday, March 11th. Present were:-

Dr. J. E. Moore, Chairman, Drs. Alyea, Clarke, Cox, Mahoney, Nelson, and Stokes, members of the Subcommittee,

Dr. Long, Committee on Chemotherapeutics and Other Agents,

Drs. Weed, Cushing, Larkey, and Forbes, National Research Council,

Colonels Simmons and Morgan, Lieutenant Colonel Turner, and Major Gordon, U. S. Army,

Captain Stephenson, U. S. Navy,

Dr. Anderson, U. S. Public Health Service,

Drs. Walker and Dochez, Committee on Medical Research,

Dr. Rostenberg, Food and Drugs Administration,

and the following invited guests:-

Drs. P. S. Pelouze, Russell Horrold, and Rogers Deakin.

The Chairman read certain correspondence from the Surgeon General, U. S. Army, to Dr. Weed, Chairman Division of Medical Sciences, which is quoted herewith:-

"Dear Doctor Weed:

February 23, 1942.

"Dr. P. S. Pelouze has just presented to us some evidence that the recommendations of the Council on the treatment of gonorrhoea may need revision in the light of recent advances in this field.

"I should appreciate your arranging for Dr. Pelouze to present his ideas to the appropriate committee of the Council for consideration.

Yours very sincerely,

S/ James C. Magee,
Major General, U. S. Army
The Surgeon General "

Dr. Pelouze then opened the discussion by stating that from observations of his own in certain Army camps, the treatment of gonorrhoea and its complications was on an unsatisfactory basis, and he expressed the opinion that the recommendations of the Subcommittee on Venereal Diseases, accepted by the Army and published in Circular Letter No. 18, March 10, 1941, were now out of date because of recent advances, and required revision. The Subcommittee agreed that such a revision was desirable. The Chairman therefore appointed Doctors Oscar Cox, P. S. Pelouze, Rogers Deakin, and Russell Horrold as a sub-group to revise the memorandum on gonorrhoea, and to present the revision for approval. If approved, the revision is to be submitted to the U. S. Army and Navy as a recommendation to replace that portion of

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Circular Letter No. 18 devoted to the diagnosis and treatment of gonorrhoea.

The revised memorandum prepared by this sub-group is herewith appended as Exhibit A.

The Subcommittee then proceeded to consider the proposal for contract of Dr. Reuben L. Kahn, University of Michigan, Ann Arbor, Michigan, for studies of the verification test (Kahn) in the detection of false positives in the serodiagnosis of syphilis. This application led to a general consideration of the subject of biologic false positive tests for syphilis. It was agreed by the Subcommittee and by the representatives of Army and Navy present that the problem was one of major importance to the armed forces as well as to the civilian population. The Subcommittee believed that it was undesirable to approach the problem from the single angle proposed by Dr. Kahn and felt that other types of investigation would likewise be of value in elucidation of the questions involved. This led to some discussion of the proposal for contract of Dr. Herbert Lund of Cleveland, previously approved by the Subcommittee on Venereal Diseases but subsequently disapproved by the Committee on Medical Research.

It was finally moved that the Chairman of the Subcommittee on Venereal Diseases be empowered to call a conference of serologists to consider the study of biologic false positive tests for syphilis. This motion was passed.

It was suggested that the following persons be asked to attend such a conference: *

Dr. John H. Stokos
Dr. Reuben Kahn
Dr. B. S. Kline
Dr. John A. Kolmer
Dr. I. Y. Mazzini
Dr. Herbert Lund

Dr. W. A. Hinton
Dr. Arthur Sanford
Dr. John A. Mahoney
Dr. Harry Eagle
Dr. Frederick Boerner

The Chairman of the Subcommittee then read certain correspondence between himself and the Surgeon General U. S. Army relating to the report of the ad hoc Commission on Venereal Diseases of the Committee on Medicine. This correspondence is herewith appended as Exhibit B.

The Chairman then read to the Subcommittee certain correspondence between Dr. A. N. Richards, Chairman, Committee on Medical Research, Dr. Lewis Weed, Chairman, Committee on Medical Sciences, and himself, dealing with the relationships of various National Research Council committees and subcommittees to the Committee on

* Subsequently, by agreement between the Chairman, Drs. Pepper and Cushing, the following names were omitted from the list of those invited: Sanford, Boerner, and Mazzini.

Medical Research. Dr. Richards' letter of February 6 to Dr. Weed has already been circulated and is therefore not herewith appended.

The Subcommittee then proceeded to a discussion of the memorandum on chemical prophylaxis of February 14, previously circulated to members of the Subcommittee, but herewith included as Exhibit C.

There was much general discussion of various topics in this memorandum. It was agreed by the members of the Subcommittee and by the Army and Navy officers present that further studies in chemical and chemotherapeutic prophylaxis were of major importance to the armed forces.

This discussion led to a motion that immediate steps be undertaken by the Subcommittee on Venereal Diseases to organize further studies in the chemical prophylaxis of venereal disease and that the Chairman be authorized to call a conference of investigators, potentially interested in such studies. This motion was passed.

It was suggested that the following persons be invited to attend such a conference: *

Dr. John Mahoney
Dr. Harry Lagle
Dr. Benjamin Miller
Dr. D. M. Pillsbury
Dr. Harry Parisor
Dr. Irvin Blank
Dr. Marion Sulzberger

Dr. Louise Pearce
Dr. H. H. Hazen
Lieut. Col. T. E. Turner
Dr. Robert L. Dickinson
Dr. Charles M. Carpenter
Dr. F. A. Fleming
Dr. Alfred Cohn
Dr. Philip Miller

and in addition a chemist, name to be suggested by Dr. Luther Kelly, American Pharmaceutical Association.

The Chairman was further authorized to approach Drs. W. Frei, Boris Kornblith, Frank C. Coombes, Everett S. Sanderson, Robert Greenblatt, Geoffrey Rake, and Murray Sanders concerning possible prophylactic experiments in lymphogranuloma venereum.

The Chairman was likewise authorized to approach Drs. Sanderson, Greenblatt, and J. A. McIntosh as to the possibility of studies in the chemical prophylaxis of granuloma inguinale.

The Chairman was also authorized to approach Drs. Frank Coombes, Orlando

* Subsequently, by agreement between the Chairman, Drs. Pepper and Cushing, the following names were omitted from the list of those invited: E. Miller, Parisor, Blank, Sulzberger, and Dickinson.

Canizares, Borris Kornblith, Harold Cole, Everett Sanderson, and Robert Greenblatt as to chemical studies in the possible prophylaxis of chancroid.

Colonel Simmons then extended to all members of the Subcommittee a cordial invitation to visit the Subdivision of Venereal Diseases, Surgeon General's Office, and to continue the close informal contacts between the members of the Subcommittee and that Subdivision. He offered to supply the members of the Subcommittee with such information as they might desire concerning progress in venereal disease control in the U. S. Army.

Lieutenant Colonel Turner said that, in view of the current shortage of mercury, the suggestion had been made to the U. S. Army that the percentage of calomel in ointment used for chemical prophylaxis be reduced from 33-1/3 per cent to 20 per cent; and asked for a recommendation of the Subcommittee on this point.

It was recommended that, in view of the discussion on chemical prophylaxis previously held and the uncertain state of knowledge at present existing; and in view further of the demonstrated efficacy of 33-1/3 per cent calomel ointment, the percentage of calomel in ointment used for prophylaxis should, pending further scientific information which may be gathered from planned investigations, be maintained at its present level of 33-1/3 per cent.

Colonel Turner then raised the issue of the provision of facilities for chemical prophylaxis for members of the armed forces in civilian hospitals. After considerable discussion of this point and of the best methods of providing such facilities, it was recommended that the Subcommittee on Venereal Diseases endorse a general policy for provision of prophylactic facilities for members of the armed forces by various civilian agencies, including hospitals.

Colonel Turner then referred to the memorandum on lymphogranuloma venereum adopted by the Subcommittee and included as Appendix G in the Minutes of the 13th meeting, and asked (a) if there was any current information which would suggest the necessity of revision of the Subcommittee's recommendation of the use of chick embryo antigen for Frei testing; and (b) for information as to sources of supply of chick embryo antigen and the uniformity of the available product.

It was agreed that all of the available information indicated that chick embryo antigen was almost as satisfactory as the best human bubo pus antigens and more satisfactory than mouse brain antigens; and that the Subcommittee therefore saw no reason to change its recommendations that chick embryo antigen be adopted for routine use in Frei testing.

It was also agreed that at present the only available source of chick embryo antigen was apparently from E. R. Squibb and Sons; and that excepting certain early batches of this antigen, the product currently supplied over the last few months was uniformly active.

The meeting then adjourned.

EXHIBIT A

PROPOSED NEW SCHEDULE FOR THE TREATMENT OF
EARLY AND LATENT SYPHILIS

In view of recent advances in the toxicity and therapeutic efficiency of antisyphilitic drugs, and in view of the specific problem of conservation of manpower confronting the Armed Forces, the Subcommittee on Venereal Diseases offers the following recommendation:-

Early (primary and secondary) and latent syphilis of any duration should henceforth be treated by an identical treatment system. This treatment may be completed within 26 weeks.

Patients with syphilis, early or latent, uncomplicated by disease or by treatment reactions, need as a rule not be hospitalized. If local conditions necessitate hospitalization, this should not be prolonged more than 5 to 7 days. Treatment should be administered by unit medical officers; or in areas where concentration of patients is feasible, in centralized ambulatory clinics established in hospitals, in the offices of Attending Surgeons, etc. Also whenever possible and to minimize lost time, treatment should be given at night or on Sundays.

The treatment schedule to be utilized is as follows:-

Week 1	Mapharsen intravenously twice weekly, total 20 injections	}	Bismuth subsalicylate intramuscularly once weekly, 5 doses
2			
3			
4			
5			
6			
7			
8			Omit bismuth
9			
10			
11			
12			
13	Omit mapharsen	}	Bismuth - 6 doses
14			
15			
16			
17			
18			
19			
20			
21	Mapharsen as in first course, twice weekly, total 20 injections	}	Bismuth 5 doses
22			
23			
24			
25			
26			

Treatment should be given regularly; no rest periods.

Mapharsen dosage: Adjusted to body weight at approximately 1 mg/kg (see appended table); minimum dose 50 mg., average 60 mg., maximum 70 mg.

Bismuth subsalicylate in oil dosage: The standard dose is 0.2 gm. of bismuth subsalicylate (not 0.2 gm. of elemental bismuth metal).

Serologic control of treatment: In patients with early syphilis a serologic test will be done at the beginning and end of this course of treatment; but treatment may be stopped whether the STS is positive or negative. After treatment the STS should be repeated 3 and 6 months later. If the test is negative at 6 months, the Syphilis Register may be closed. If the test is positive at 6 months, the patient should be referred to a station or general hospital for consultation.

In patients with latent syphilis the STS need not be repeated after the start of treatment; and the Syphilis Register may be closed when treatment is completed.

Spinal fluid examination: Should be performed in patients with early syphilis at the end of this course of treatment, or as soon as possible thereafter; but in any event before the Syphilis Register is closed. In apparent latent syphilis, spinal puncture should be performed before treatment or as soon as possible thereafter, but in any event before the Syphilis Register is closed.

Post treatment follow-up and observation: In patients with early syphilis, the complication to be anticipated after completion of treatment is infectious relapse (most of these within the first 6 months). To facilitate the recognition of such cases, the following measures will be adopted during and after treatment:

(1) The patient will be handed a folder describing the possible forms of infectious relapse; warning him to report such manifestations promptly to his Medical Officer; and describing precautions for the protection of others.

(2) Periodic physical inspection by Medical Officers will include not only

the genitalia (as in routine venereal inspection) but also the anus, the buccal mucosa, and skin.

Complications or Relapse: In the event of any complication of treatment (serious treatment reactions) or any evidence of relapse, clinical or serologic, the patient should be at once transferred to a Station or General Hospital for consultation.

Separation from the Service: At contemplated discharge, the status of every patient with syphilis, acquired before or after entrance into the Armed Forces, will be completely reevaluated.

EXHIBIT A

To the Minutes of the 14th Meeting
Subcommittee on Venereal Diseases

SUGGESTED REVISION ARMY CIRCULAR LETTER NO. 18
Dated March 10, 1941.

A. Diagnosis of Gonorrhea in the Male.

(1) A diagnosis of gonorrhea must not be made in the absence of laboratory confirmation. (In emergencies, where laboratory facilities are not available within 24 hours, patients with acute urethral discharge should be treated as for gonorrhea. Before the institution of treatment, however, smears should be taken for subsequent laboratory study).

(2) In the presence of urethral discharge the diagnosis of gonorrhea must depend upon the finding of typical gonococci by the Gram method of staining. (No single-stain method should be used).

(3) Where urethral discharge is not present a diagnosis frequently can be made by a study of the sediment of the first glass of urine. In the later stages of the disease and, if there is no contraindication to the required procedures, the sediment of the urine passed immediately after digitally stripping the prostate, Cowper's glands, and the urethra, will serve the same purpose.

B. Diagnosis in the Female.

(1) Diagnosis should be based on

(a) History

1. SYMPTOMS (dysuria, vaginal discharge, vulvar pruritis, pelvic inflammation, acute arthritis).

2. Exposure to known case.

3. Accusation of having infected another.

(b) Clinical examination, especially abdominal, pelvic and rectal,

(Particularly important in chronic cases).

(c) Gram stain of secretion from urethra, Bartholin's glands and the rectum.

(d) Culture, which always should be performed if smear findings do not corroborate history and physical findings.

C. Treatment of Gonorrhea in the Male and Female.

(1) Upon the establishment of a diagnosis in either sex, chemotherapy should be started.

(a) Sulfathiazole is at present the drug of choice.

(b) Administer 1 gram (15 grains) 4 times a day for 5 days.

(c) A second course should be given if there is evidence of persistence or recurrence of the disease. There should, however, be a lapse of 5 days between the two courses of medication.

(d) Patients in whom the gonococcus is present after this second course should be transferred from the Station to a General Hospital.

D Procedure in General Hospitals.

(1) It is recommended that sulfonamide resistant cases be given controlled, sustained fever therapy preceded by sulfathiazole.

(2) Patients not cured by this means should be placed upon local treatment.

E. Local Treatment in Anterior Urethritis.

(1) Daily anterior urethral injection of not more than 6 c.c. of a 5 per cent solution of mild protein silver or 0.5 per cent of strong protein silver. (Retain for 5 minutes).

- (2) The frequency of injection should be decreased as the discharge disappears.

F. Local Treatment of Posterior Urethritis.

- (1) Stop all local treatment until acute symptoms have subsided.
- (2) Give hot hip baths for painful urination.
- (3) When the second glass of urine has been clear and the first glass nearly so for 2 weeks, extremely gentle prostatic stroking should be tried. (If this causes a recrudescence of symptoms, it should not be repeated for 1 week. If not, the gland should be gently stripped at 3 or 4 day intervals).
- (4) Infections of Cooper's glands should be searched for and, if these glands are palpable, they should be gently kneaded between the intra-rectal index finger and the thumb against the perineum at the same time the prostate is treated.
- (5) When the status changes from gonococcal to nonspecific prostatitis, as proved by smears and cultures, the patient should be discharged. In most patients this occurs after about 6 weeks of prostatic massage, providing there are no other complications.
- (6) No instruments of any type should be passed into the urethra while the gonococcus is present.
- (7) All patients with gonorrhoea should have a serologic test for syphilis done on admission and a follow-up test later in the disease. If only one is carried out, it should be performed 3 - 4 months after the onset of gonorrhoea.

G Local Treatment in the Female.

- (1) In the early stage, external cleanliness only; no douches.
- (2) In acute pelvic inflammatory disease:
 - (a) Bed rest
 - (b) Ice bags to abdomen
 - (c) Keep bowels open. (If enemas are necessary, clean anal region carefully before inserting tube).
 - (d) In chronic infections, direct treatment to the residual foci.

H. Determination of Cure in the Male.

- (1) Patients whose symptoms have disappeared as the result of chemotherapy may have tests of cure carried out as early as the third day after medication is discontinued.
- (2) Patients whose infections have remained in the anterior urethra despite chemotherapy should have tests of cure 3 weeks after all symptoms have disappeared.
- (3) Patients whose treatment has included prostatic massage should have studies of their secretions made after the first few prostatic stripings, and should be dismissed from treatment after 3 successive negative studies made at weekly intervals.
- (4) The test of cure rests upon the inability to demonstrate the gonococcus in any of the urogenital fluids by smears and cultures. These should be obtained in the manner previously described. The prostatic secretion should be included in the study of all types (three successive negative studies at weekly intervals).

I Determination of Cure in the Female.

- (1) Do pelvic examination for the presence of masses.
- (2) Examine smears (Gram stain) from urethra, cervix, and Bartholin's glands once every two weeks for 3 months.
- (3) Confirm negative smears by cultures from these regions.
- (4) To obtain materials for smears and cultures massage urethra and Skene's glands, obtaining secretion with small cotton-wrapped applicator. Pass bivalve vaginal speculum without lubricant, expose cervix, clean cervical canal with cotton applicator, squeeze cervix between ends of speculum blades and obtain expressed fluid for smear and culture.

Squeeze Bartholin's glands between thumb and finger and obtain secretion at openings of the ducts.
- (5) If no gonococci are found in 3-4 months of post-treatment study, discharge patient as cured.

EXHIBIT B

The Subcommittee on Venereal Diseases recommends the following revision of that portion of Army Circular Letter No. 18, devoted to gonorrhoea.

DIAGNOSIS AND TREATMENT OF GONORRHEA

A. Diagnosis in the Male

(1) A diagnosis of gonorrhoea must not be made in the absence of laboratory confirmation. Treatment for gonorrhoea should be started at once if the patient has an acute purulent urethral discharge, but material should be obtained before treatment is begun for subsequent laboratory study (smear and/or culture).

(2) Active Gonorrhoea

(a) The detection of Gram-negative intracellular diplococci in smears of the urethral exudate, or in smears of the centrifuged sediment of the first glass of urine, establishes the diagnosis of gonococcal infection.

(3) Inactive Gonorrhoea

(a) The detection of Gram-negative intracellular diplococci in smears of the exudate obtained by digital stripping of the prostate, Cowper's glands, and the urethra, or in smears of the centrifuged sediment of urine passed after stripping the prostate, Cowper's glands, and the urethra, or in positive cultures of material so obtained, establishes the diagnosis of gonococcal infection.

B. Diagnosis in the Female

(1) A diagnosis of gonorrhoea must not be made in the absence of laboratory confirmation. (Treatment for gonorrhoea should be started at once in women who have evidence of this disease, even though laboratory studies are negative or not available. If laboratory facilities are not available, material for subsequent laboratory studies should be obtained before treatment is begun.)

(2) The detection of Gram-negative intracellular diplococci in smears of material obtained from any of the following: the urethra, Skene's glands, and

Exhibit B- 2

the cervix (and from Bartholin's glands and the rectum, when clinical symptoms so indicate); or positive cultures of material so obtained, establishes the diagnosis of gonococcal infection. (Caution. the normal genital flora and that of non-specific infections may contain organisms that on smear closely resemble gonococci. Therefore, cultural methods should be utilized when possible.)

C. Serologic Tests for Syphilis.

(1) All patients with gonorrhea should be given a serologic test for syphilis on admission, a follow-up test before being discharged to duty, and if possible a final such test three months later.

D. Treatment of Gonorrhoea in Station Hospitals (Male and Female.)

(1) Treatment should consist of not more than two courses of chemotherapy.

(a) Sulfadiazine and sulfathiazole are each highly efficient, and in the dosage recommended cause almost no toxic manifestations. Either of these compounds is recommended as the drug of choice. Sulfapyridine, although nearly as efficient as sulfathiazole or sulfadiazine, should be used only if the other compounds are not available because of its high incidence of toxic manifestations. Sulfanilamide is less efficient than the other sulfa compounds and should not be used unless no other sulfonamide is available.

(b) The recommended dosage for sulfadiazine and sulfathiazole is 1 gram (15 grains) 4 times a day for 5 days, and the recommended dosage for sulfapyridine or sulfanilamide is 1 gram (15 grains) 3 times a day for 5 days.

(c) A second course of the drug, in the same dosage, should be given if there is evidence of persistence or recurrence of the disease. There should, however, be a lapse of 5 days between the two courses of medication.

(d) Personnel in whom the gonococcus is present after the second course,

Exhibit - 2

er who have not made a satisfactory clinical response, should be transferred to a general hospital.

(e) Local treatment to the urethra should be carried out only in General Hospitals.

E. Treatment of Gonorrhoea in General Hospitals. (Male and Female)

(1) It is recommended that sulfonamide-resistant cases be given 10 hours of controlled, sustained fever therapy (where such therapy is available) preceded by 18 hours of chemotherapy. Although this form of treatment carries a definite risk, results are superior to those of local treatment. Patients not cured by this means should be placed upon local treatment.

(2) Local Treatment in the Male

(a) Daily anterior urethral injection of not more than 6 c.c. of a 5 per cent solution of mild protein silver or 0.5 per cent of strong protein silver. (Retain for 5 minutes).

(b) All urethral injections to be administered by a medical officer or trained attendant; not by patient.

(c) The frequency of injection may be decreased as the discharge diminishes, as determined by the routine use of the two-glass urine test.

(d) Stop all local treatment if the patient develops acute symptoms of posterior urethral infection, such as urgency, painful or marked frequency of urination, or perineal or rectal pain; and confine treatment to hot Sitz baths. When acute symptoms have subsided, resume anterior urethral injections and continue them until prostatic stroking is begun.

(e) Extremely gentle prostatic stroking should be tried when the second glass of urine has been clear, and the first glass nearly so, for 2 weeks. If

this causes pain during massage or a recrudescence of other symptoms, it should not be repeated for 1 week, or until the symptoms have subsided. If not, the gland should be gently stripped at 3 or 4 day intervals, and smears of the prostatic secretion examined every 2 weeks.

(f) Infections of Cowper's glands should be searched for and if these glands are palpable, they should be gently kneaded between the intra-rectal index finger and the thumb against the perineum at the same time the prostate is treated.

(g) No instruments of any type should be passed into the urethra while gonococci are present.

(3) Local Treatment in the Female.

(a) Active stage with vaginal discharge.

1 External cleanliness is important.

2. The curative value of hot douches is not known, but if given with reasonable care and at not more than 2 feet of water pressure, they promote hygiene and may add to the patient's comfort.

(b) Acute pelvic inflammatory disease.

1. Bed rest.

2. Ice bag to abdomen.

3. Keep bowels open. (If enemas are necessary, clean anal region carefully before inserting tube.)

F. Determination of Cure in the Male. (Uncomplicated cases)

(1) Patients whose symptoms have disappeared as the result of chemotherapy may have tests of cure started on the third day after medication is discontinued.

(2) Cure is determined by inability to demonstrate gonococci in any of the urogenital fluids by smears or cultures. This includes the examination of the

prostatic secretions. Patients should be discharged from observation after 3 negative studies at weekly intervals.*

G. Determination of Cure in the Male. (Sulfonamide-resistant cases)

- (1) Patients whose symptoms have disappeared as the result of prolonged fever therapy may have tests of cure started on the second day following the treatment.
- (2) Patients whose infections have remained in the anterior urethra despite chemotherapy and artificial fever should have tests of cure begun 3 weeks after all symptoms have disappeared.
- (3) Patients whose treatment consists of prostatic massage should have tests of cure started at no later than 6 weeks after prostatic massage is begun.
- (4) Post-gonococcal prostatitis should be considered non-specific after 6 weeks of prostatic treatment, if the tests of cure are negative. Patients with non-specific post-gonococcal prostatitis should be discharged to duty.
- (5) Cure is determined by the inability to demonstrate the gonococcus in any of the urogenital fluids by repeated smears and cultures. Material for these studies should be obtained in the manner previously described in A. (3) (a). The prostatic secretion should be included in the study of all types of infection. Three successive negative studies at weekly intervals constitute practical evidence of cure.
- (6) Tests for cure should be carried out on a duty status.

H. Determination of Cure in the Female (Uncomplicated cases)

- (1) Patients whose symptoms have disappeared as the result of chemotherapy may have tests of cure begun on the third day after medication is discontinued.

* Patients who become symptom-free by the fifth day may be discharged to duty if smears and cultures of the urogenital fluids are negative on the eighth day. However, these should return to the hospital for 2 subsequent studies at weekly intervals.

(2) Cure is determined by:

(a) Absence of tender masses or points of tenderness in the pelvis.

(b) Inability to demonstrate the gonococcus by smears and cultures in material obtained from the urethra, Skene's glands, and the cervix. Such tests should be repeated every 2 weeks for 3 months and, if all are found to be negative, the patient should be discharged from observation. These tests should be carried out on an ambulatory basis.

(c) To obtain material for smears and cultures, massage the urethra and Skene's glands, obtaining secretion with small cotton-wrapped applicator. Pass bivalve vaginal speculum without lubricant, expose cervix, clean vagina and cervical canal, squeeze cervix between ends of speculum blades, and obtain expressed fluid on cotton applicators for smear and culture.

I. Determination of Cure in the Female. (Sulfonamide-resistant cases)

(1) Patients whose symptoms have disappeared as the result of prolonged artificial fever may have tests of cure begun on the second day after treatment. The tests of cure are the same as those recommended for female patients in uncomplicated gonorrhoea.

(2) Patients under local treatment should have smears and cultures done at least every 2 weeks. If these studies remain consistently negative for 3 months, and if there are no demonstrable complications, the patient should be discharged from observation.

EXHIBIT B

To the Minutes of the 14th meeting Subcommittee on
Venereal Diseases

804 Medical Arts Building
Baltimore, Maryland.

February 19, 1942.

Surgeon General
U. S. Army
War Department
Washington, D.C.

Sir:

On February 17th I was invited to attend a meeting of the Committee on Medicine, National Research Council, to hear the report of the ad hoc Commission on Venereal Diseases. The contents of this report would be of great interest to the Subcommittee on Venereal Diseases, National Research Council. I respectfully request that I be furnished with a copy of the report and that I be given permission to bring it to the attention of the members of that Subcommittee at its next meeting.

Respectfully,

S/ J. E. Moore, M.D., Chairman,
Subcommittee on Venereal Diseases.

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WAR DEPARTMENT
OFFICE OF THE SURGEON GENERAL
WASHINGTON

February 28, 1942.

Dr. J. E. Moore, Chairman
Subcommittee on Venereal Diseases
National Research Council
804 Medical Arts Building
Baltimore, Maryland.

Dear Doctor Moore:

Due to a temporary absence, I have been delayed in answering your letter of February 19, 1942, in which you requested a copy of the report of the Committee on Medicine of the National Research Council on the venereal disease program in the Army. I am pleased to comply with this request and would like you to accept it as Chairman of the Subcommittee on Venereal Diseases, as we had intended to send the report to that group for their information and for any additional comments which they might care to make.

The Committee on Medicine, rather than the Subcommittee on Venereal Diseases was asked to make this survey of the Army's program because the latter group had been so closely identified with the program through its many valuable recommendations to my office during the past year, that it was believed that a report rendered by the Committee on Medicine might better serve the purpose intended, than would a report by a group closely associated with the development of the venereal disease program.

I feel sure that the members of your Subcommittee will be glad to know that since the declaration of war the increase in officer personnel has enabled us to re-inaugurate the policy of assigning special Venereal Disease Control Officers to the various important military commands, including General Headquarters, and the headquarters of Communications Zones, Field Armies, Divisions, Corps Areas, Departments, and camps with twenty thousand or more troops. A copy of the directive putting this policy into effect is enclosed. The Subdivision of Venereal Disease Control in my office has also obtained the services of Lt. Colonel Thomas B. Turner, Medical Corps, and he and Major Gordon are now engaged in the procurement of officers trained in the control of venereal disease to fill the positions mentioned above. We feel that the assignment of this additional personnel should produce tangible results.

I wish again to assure the Subcommittee on Venereal Diseases that we deeply appreciate the very real assistance which they have rendered to the Army through their recommendations. Problems relating to venereal disease will doubtless continue to arise, and I hope that by working even more closely together during this wartime period we may further improve our program for the control of venereal disease in the United States Army. In this connection, I would be pleased to have members of the Subcommittee visit the Subdivision of Venereal Disease at any time, and it is suggested that by the maintenance of closer informal contacts with this Subdivision and its current activities, the members of the Subcommittee will gain a better insight into our problems and be in a position to render even more helpful advice.

Yours very truly,

S/ James C. Magee, Major General U. S. Army
The Surgeon General

804 Medical Arts Building
Baltimore, Maryland.

March 4, 1942.

Major General James C. Magee,
The Surgeon General U. S. Army,
War Department
Washington, D.C.

Dear General Magee:

Thank you very much for your courteous letter of February 28, 1942, transmitting to me as Chairman of the Subcommittee on Venereal Diseases the report of the ad hoc Commission of the Committee on Medicine, National Research Council, appointed to carry out a survey of the venereal disease control program of the Army and the existing venereal disease conditions of the Army. I shall take great pleasure in bringing this confidential report to the attention of the members of the Subcommittee on Venereal Diseases.

The members of that committee will, I know, be highly gratified by the re-inauguration of the policy of assigning special venereal disease control officers to various important military commands and of the progress already made in this direction.

The members of the Subcommittee will also be gratified by your appreciation of their several recommendations and by your suggestion that the relationships between the Subcommittee and your office be maintained by close informal contacts of members of the Subcommittee with your Subdivision of Venereal Diseases.

Respectfully,

S/ J. E. Moore, M.D., Chairman,
Subcommittee on Venereal Diseases.

Cc: Members of the Subcommittee
on Venereal Diseases.

EXHIBIT C

MEMORANDUM

February 14, 1942.

To all Members
Subcommittee on Venereal Diseases
National Research Council

The chemical prophylaxis of the venereal diseases remains in a most uncertain state. The value of station prophylaxis as carried out by Army and Navy, utilizing soap and water, silver proteinate solutions, and 33 per cent calomel ointment, has been more or less clearly demonstrated for syphilis, gonorrhea, and chancroid.

There is literally no available information, especially as to gonorrhea but also as to syphilis, as to the value of tube (self-administered) prophylaxis; as to whether silver proteinate or other antiseptics in an ointment or jelly base are effective; as to whether prophylactic effect may depend on mechanical factors, or on such factors as pH, etc., etc.

There is no information whatever as to the prophylaxis of lymphogranuloma venereum, or of granuloma inguinale.

Chemotherapeutic prophylaxis (with bismuth) has been demonstrated to be effective in syphilis; but there are no data as to the chemotherapeutic prophylaxis of gonorrhea (with sulfonamides).

The need of Army and Navy, and of the Food and Drug Administration of the Department of Agriculture for further information on these and other points seems urgent. For this reason, I have prepared the following brief summary of present and desired knowledge. The remainder of this memorandum is purposely triple spaced; and two copies of it are sent to each of you. Would you be good enough to review it in detail, to make such corrections, alterations, or additions in it as you see fit, and to return to me promptly one copy so corrected?

It is planned that the entire subject be reviewed at a meeting of the Subcommittee in the near future, with the possibility in mind that experimental and clinical studies might perhaps be stimulated by the Subcommittee.

Very truly yours,

J. E. Moore, M.D.,
Chairman.

Cc: Drs. Stokes, Alyea, Cox, Clarke,
Nelson, Mshoney, Vonderlehr,
Long, Pepper, Weed, Larkey and
Eagle. Capt. Stephenson, Lt.
Col. Turner.

3) What are the time limits of effectiveness?

4) Is activity dependent on pH only?

New information desired in experimental animals:-

1) Are the trivalent arsenicals effective in ointment or jelly base?

2) Are bismuth compounds ditto?

3) What is the effect of prophylaxis by electrophoresis (Perreyra)?

4) Are acid jellies (contraceptive type) effective?

5) Does mechanical coating with oil or ointment protect?

Suggestion:- that the experimental laboratories of Mahoney, Eagle, Kolmer, Carpenter, Fleming, Turner and, if available, others be asked to undertake these problems in rabbits, and if possible monkeys.

GONORRHEA

Known:- that silver proteinate solutions (2% protargol, 10% argyrol) confer some protection if used within 1-2 hours after exposure.

Source of knowledge:- clinical data secured from Army and Navy records.

Uncertain points as to silver protinate solutions:-

1) Do they confer certain protection if used within proper time limits?

2) What are the time limits of effectiveness?

New information desired:-

- 1) Are other antiseptics equally or more effective in solution (acriflavine, silver picrate, etc.) ?
- 2) Are these or other antiseptics effective in ointment or jelly base? In what concentrations? And in what sort of base?
- 3) What is effect of sulfathiazole or sulfadiazine ointment or jelly?
- 4) What is effect of mechanical coating with oil (progynsil like substances) in male and female?
- 5) What is effect of pH (acid jellies of contraceptive type)?
- 6) Prophylaxis by electrophoresis?

Suggestions:-

- 1) Preliminary in vitro studies
- 2) That Army and/or Navy, or failing this, penitentiary physicians, conduct controlled experiments with human volunteers. If this was justifiable with a non-treatable disease with a high mortality rate (yellow fever), surely it is justifiable with a non-fatal easily treatable disease such as gonorrhoea.
- 3) Failing human experimentation, that selected Army and

Navy units, preferably those stably located in various countries, be instructed deliberately to abandon silver proteinate prophylaxis and to use alternative and specially designated procedures, records of exposures and infections to be kept on standard forms and forwarded to the Surgeon General's offices for comparative evaluation.

LYMPHOGRANULOMA VENEREUM

Known: Nothing

Suggested:-- autoinoculation experiments in male persons with acute bubonic lymphogranuloma. It is not known whether these would be infective, since the patients' own immunity might protect him. If infective, inoculated areas might be treated with various prophylactic substances, as in auto-inoculated chancroid.

Certain selected hospitals (University of Georgia, Bellevue, and perhaps others) should be invited to participate, all patients to be hospitalized.

If human experimentation is impossible or inconclusive, the in vitro effect of potentially prophylactic substances on the virus might be tried, checked by egg yolk-sac or mouse inoculations (suggested laboratories: -- Squibb Research, Army Medical School, Rockefeller Institute, University of Rochester).

Is immunization with live virus possible?

GRANULOMA INGUINALE

Known: Nothing

Suggested:- Is granuloma inguinale uniformly and regularly transmissible to any animal species? If so, effectiveness of prophylactic substances could be tried experimentally.

Is granuloma inguinale auto-inoculable in human beings? If animal experimentation is impossible (but not until this impossibility has been demonstrated) auto-inoculation and prophylactic experiments should be tried on volunteer infected persons.

Senderson and Greenblatt (University of Georgia) should be asked to undertake animal experiments.

CHANCROID

Known: that soap and water will probably prevent infection; that calomel ointment probably will not (based on human auto-inoculation experiments in 5 persons only - Moore, 1920).

Suggested:- auto-inoculation and prophylactic experiments on a larger scale in persons infected with chancroid and in volunteers.

Should be carried on only in hospitals in which diagnosis of chancroid can be bacteriologically proved (Johns Hopkins, University of Georgia, Bellevue, and others).

Summary of available information as to chemical prophylaxis of venereal disease; and suggestions for further study.

SYPHILIS

Known:- that 33-1/3 per cent calomel ointment will protect if locally applied within 1 - 4 hours after exposure, perhaps as long as 8 hours; that soap will protect if applied immediately.

Source of knowledge: as to calomel, animal and human experimentation, Army and Navy clinical data. As to soap, inadequate animal experiments, clinical experience.

Uncertain points regarding calomel ointment requiring further study in

experimental animals:- 1) Is action of calomel ointment local (chemical) or systemic (chemotherapeutic) (Mahoney's experiments), and if the latter, what is the protective dose in mg/kg in rabbits?

2) More accurate delineation of time limits of effectiveness after exposure

3) Is effectiveness of calomel ointment diminished or enhanced by addition of other (presumably gonococidal) substances?

Uncertain points as to soap requiring further study:-

1) Are soaps actually effective in experimental animals?

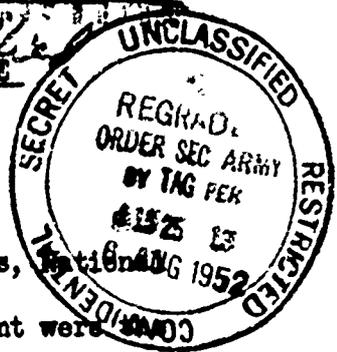
2) If so, do different types of soap vary in effectiveness?

NOT FOR PUBLICATION
WITHOUT PERMISSION OF
NATIONAL RESEARCH COUNCIL ON VENEREAL DISEASES

V. D. 42-1

THE MINUTES OF THE THIRTEENTH MEETING OF THE SUBCOMMITTEE
ON VENEREAL DISEASES OF THE NATIONAL RESEARCH COUNCIL

January 13, 1942.



The 13th meeting of the Subcommittee on Venereal Diseases, National Research Council, was held in Washington, January 13, 1942. Present were following members of the Subcommittee: Doctor Moore (Chairman), Doctors Stokes, Cox, Alyea, Mahoney, and Nelson; Doctors Weed and Cushing, Division of Medical Sciences, National Research Council; Doctors Pepper and Morgan of the Committee on Medicine, National Research Council; Doctors Larkey and Forbes of the National Research Council; Doctors Walker and K. Turner of the Committee on Medical Research; Colonels Hillman, Simmons, Callender, Lieut. Colonel Kimbrough and Major Prentiss, U. S. Army; Captain Stephenson, U. S. Navy; Dr. McCown of the American Red Cross; Assistant Surgeon General Vonderlehr, U. S. Public Health Service; Mr. J. S. Owens, Regional Representative, Division of Social Protection, FSA; Dr. T. B. Turner, Johns Hopkins School of Hygiene and Public Health; and the following guests all invited by the Subcommittee to discuss the intensive arsenotherapy of early syphilis: Dr. Harold T. Hyman, Dr. Bernard Kaplan, Dr. Herbert Rattner, Dr. Bruce Webster, Dr. Evan Thomas, and Doctors David Elliott and Harry Eagle, both of the U. S. Public Health Service.

As the first item on the agenda of the meeting the entire morning session and a portion of the afternoon was devoted to a discussion of the intensive arsenotherapy of early syphilis. This was brought about at the request of the Surgeon General, U. S. Army, on the basis of the following correspondence:

FROM: Dr. Harold T. Hyman
TO: Major General James C. Magee, Surgeon General, U. S. Army
DATE: December 29th, 1941.

FILE
Med Res & Dev Bd
11-2-57
DATE
INITIALS

"Sir:

Through the good offices of the Secretary of War, I met with Brigadier General Snyder, Colonel Hillman, and Lieutenant-Colonel Simmons with reference to the possibility of introducing five day treatment of syphilis into the armed forces.

It is my belief that such a step would appreciably lower the man-days lost in treatment and eliminate the disturbances relative to the procurement of the weekly injections spaced over a period of eighteen months.

The treatment risk by the intensive method seems to be inappreciably greater than that of conservative treatment. The therapeutic results (100 per cent "cure" in sero-negative and sero-positive primary syphilis) exceed any previously described.

The production of dark field negativity on the second day of treatment and at all times thereafter eliminates the possibility of innocent infection and renders unnecessary the measures taken to prevent this complication.

I am not satisfied that the subject of intensive treatment has ever been adequately presented to those of you in whose hands rest the decisions relative to medical policies. The committees on which you rely include no one of us who has had actual first-hand experience with the method.

I would therefore respectfully request of you that you call a meeting for the specific purpose of discussing the pros and cons of five day treatment of early syphilis. I would suggest that that meeting be attended by those who are, as yet, unconvinced of the merits of our work, notably Dr. J. E. Moore, but also those of us who are actively engaged in this work. This latter group would include Dr. David Elliott and Dr. John Mahoney of the United States Public Health Service; Dr. Francis Blake of Yale University; Dr. Bernard Kaplan and Dr. Charles Sweet of Sing Sing Prison; and Dr. Herbert Ratner of Chicago.

Yours,

Harold Thomas Hyman, M.D."

FROM Dr. Harold T. Hyman

TO The Honorable Henry L. Stimson, Secretary of War

DATE December 29, 1941.

"Sir:

I enclose a copy of my letter to the Surgeon General of the Army.

I am deeply grateful to you for making possible my interview with Brigadier General Snyder. In every particular, I met with gratifying cordiality and a scientific spirit that will go far to a satisfactory understanding of our mutual problem.

Yours,

Harold Thomas Hyman, M.D."

FROM: Col. C.C. Hillman, M.C. -3-
TO: Dr. Lewis H. Weed, Chairman, Division of Medical Sciences
Date: January 1, 1942.

"Dear Doctor Weed:

There are inclosed herewith copies of communications from Dr. Harold T. Hyman, which are self-explanatory.

In order that this office may have the considered opinion of the Subcommittee on Venereal Diseases concerning the safety and efficiency of the five-day treatment of syphilis, it is requested that Doctor Hyman be permitted to present the matter in person to the committee at an early date. It is recommended also, to insure full presentation of the matter, that the others whom Doctor Hyman mentions as having had experience with this method be invited to attend.

Sincerely yours,

C. C. Hillman,
Colonel, Medical Corps,
Assistant. "

The Chairman first called upon Dr. Harold T. Hyman to read a paper, the manuscript whereof is appended to these Minutes as Appendix "A".

The Chairman next called upon Dr. Bernard Caplan of Sing Sing Prison, Ossining, New York, who has used the five day continuous drip method of treatment, or some modification if it, in a group of patients with late syphilis. The statistical data presented by Dr. Kaplan are appended to these Minutes as Appendix "B". The results obtained by Dr. Kaplan may be summarized as follows:

There have been no cases of toxic encephalopathy and no deaths. The general effect of treatment on the serologic tests in early latent syphilis has been a slow fall in reagin content over a period of 12 to 18 months. In late latent syphilis there has been no immediate serologic effect of treatment. In early asymptomatic neurosyphilis the cell count and protein content of the spinal fluid has generally decreased, but in late asymptomatic neurosyphilis there has been no immediate effect.

Dr. Kaplan was asked his opinion as to the desirability of adoption of this method of treatment by the armed forces, and declined to express an opinion since he had had no experience with its use in the early stages of the disease.

Dr. Herbert Rattner of the Cook County Hospital, Chicago, next reported that he had had 18 months' experience with the method in 310 patients, two-thirds

of them were men, one-third women, their ages ranging from 16 to 52. He has utilized the New York technique of five-day continuous intravenous drip with a dosage of 1200 milligrams of mapharsen, regardless of body weight. As to serious reactions there have been no deaths, but 3 toxic encephalopathies (2 of which with hemiplegia) and one patient with anuria, uremia, hepatitis, and pericarditis. Of these 4 serious reactions all patients recovered without residuals.

Dr. Rattner reported on the clinical results of 200 patients treated 6 months or more ago. Of these 44 were lost from observation, and of these 44 lost patients, 10 were showing serologic improvement at the time the patient was last seen. One hundred fifty-six patients were evaluated with a minimum observation period of 6 months. Of these 106 were "cured". In 33 the blood serologic test was falling toward normal but had not yet become negative. (16 of these in a 4 - 6 months' period, and 17 in a period of 6 months or over). Seventeen patients were rated as "unsatisfactory". Of these 6 were regarded as reinfection or superinfection, 2 as clinical relapse, and 9 as serologic relapse. Thirteen of these 17 unsatisfactory cases have now been retreated and, of these, 6 are now apparently "cured", while 7 are improving. Included in the total series are 11 pregnant women, all of whom were treated without difficulty, and 7 of whom have now been delivered of normal babies. Two hundred eighty five spinal fluids have been examined all normal.

In brief summary, of the 156 patients evaluated, Dr. Rattner regards 154 as either "cured" or tending toward "cure".

Asked for an opinion as to the desirability of the adoption of the method by the armed forces, Dr. Rattner's feeling was that the method was advisable and that while in Chicago it was regarded as still in the experimental stage, it was now approaching, if it had not actually reached, a point at which its routine adoption seemed desirable.

Dr. Bruce Webster of the New York Hospital next reported that of the original series of patients treated at the Mount Sinai Hospital, the clinical follow-up was divided with every alternate patient between his own clinic at the New York Hospital and that of Dr. Evan Thomas at Bellevue Hospital. Referring to the 100 1200 milligram patients reported in Dr. Hyman's paper (see Appendix "A") Dr. Webster reports on the status of 50 of these as of January 10, 1942. Unfortunately Dr. Webster's statistical presentation was less clear than might have been desired and at the date of preparation of these minutes he has not yet submitted a written analysis. (If such an analysis is received before the minutes are circulated, it will be included as the last Appendix). As nearly as can be gathered, however, Dr. Webster's report was based on 55 patients, 50 of whom were included among the 100 patients given 1200 milligrams, referred to in Dr. Hyman's report; and 5 of whom had been retreated with a dosage of 1200 milligrams after an original treatment with a smaller dosage which had failed. Included also were 3 of the original 50 patients in whom a 1200 milligram dose had failed and who had been retreated. Thus Dr. Webster's report was based on 58 treatments of 1200 milligrams given to 55 patients. The status of 26 of these cases was known as of January 10, 1942. Of these 26, 6 were failures (4 with infectious relapse or reinfection, one with a positive spinal fluid, and one with a serologic relapse). Of the 32 patients lost from observation prior to January 10, 1942, it was impossible for Dr. Webster to evaluate success or failure as of the time the patients were last seen, but at least 12 of these were still seropositive at the time of the last visit. This seemed to make a total of 18 unsatisfactory results among 55 patients, these 55 being drawn from the same material as reported in Dr. Hyman's paper. Here only 9 unsatisfactory results were reported among 100 patients. The discrepancy between the reports of Doctors Webster and Hyman could not be resolved at the meeting; and it was suggested and agreed to that on the return of these several observers to New York, agreement be arrived at, if possible, by a meeting of the now disbanded Intravenous Drip Committee or, failing this, by a meeting of Doctors Hyman, Webster, and Thomas.

Dr. Webster asked for an opinion as to the desirability of adoption of this method by the armed forces, did not favor it. He regards the method as still so much in the experimental stage as to be unsuitable for use in his own hospital (The New York Hospital).

Dr. Evan Thomas of Bellevue Hospital next reported. Dr. Thomas had not prepared a survey of the original patients treated at the Mount Sinai Hospital and followed at Bellevue; and was able to state only that in such patients an approximate 15 per cent of relapses had been observed in the patients treated at Mount Sinai Hospital. This per cent of relapse, however, was based on the material as a whole (small doses as well as the 1200 milligram dose on which Dr. Hyman's report is based). Dr. Thomas commented on the statistics prepared by Dr. Leifer for Dr. Hyman that he (Thomas) would not have adopted the statistical method used; and that he based the discrepancy between Doctors Hyman and Webster to be accounted for by the apparent fact that in the Mount Sinai material an original relapse was not so called if the patient had been successfully retreated. Dr. Thomas further pointed out that the intravenous drip committee had held no meeting for over a year, and that Dr. Webster and himself had not been called upon for information as to the status of the cases followed in the New York or Bellevue Hospitals within this period of time. Dr. Thomas agreed further, however, to bring the committee up to date on the Mount Sinai cases followed at Bellevue.

Dr. Thomas then proceeded to report on 694 patients with early syphilis treated by himself at Bellevue Hospital by a multiple dose modification of the method of intensive arsenotherapy, these patients being divided into 275 treated with mapharsen alone, and 419 treated with a combination of mapharsen plus fever. The data presented by Dr. Thomas are appended herewith as Appendix "C".

Asked for an opinion as to the desirability of the adoption of the method by the armed forces, Dr. Thomas said that he believed the intensive arsenotherapy of early syphilis by any modification to be still entirely in the experimental stage and to be suitable for administration only to patients who volunteered for it. He did not advise the five-day intravenous drip of 1200 milligrams of mapharsen as a routine hospital procedure. He did not believe that the best type of intensive arsenotherapy of early syphilis had been as yet discovered and felt that various workers were still groping.

Dr. David Elliott next reported on a cooperative experiment being carried out in 10 hospitals in the midwest under the auspices of the U. S. Public Health Service. These are the Louisville City Hospital, the St. Louis Isolation Hospital, the Indianapolis City Hospital, Broadlawns Hospital of Des Moines, Iowa, the University Hospital of Minneapolis, the Wisconsin General Hospital of Madison, the Herman Keefer, and the Henry Ford Hospitals of Detroit, the University Hospital of Ann Arbor, Michigan, and the Cook County Hospital of Chicago. These several hospitals are all utilizing the original five-day intravenous drip method or some modification of it, and are reporting their results to Dr. Elliott, the regional representative of the U. S. Public Health Service in Chicago. It was not possible for Dr. Elliott to provide a detailed report of the patients so far treated, since conference of the representatives of these several hospitals is held at approximately 6 month's intervals, the next conference being set for January 16, 1942. (i.e., only 3 days from the date of the meeting of the Subcommittee on Venereal Diseases). The results to be collated at the January 16th conference are obviously not therefore available. However, Dr. Elliott reported that in the ten hospitals under discussion 907 cases of early syphilis have so far been treated, of which 73 have been lost from observation, 491 have so far achieved sustained seronegativity, 39 (4.3 per cent) have developed infectious relapse, and 304 are still seropositive under observation.

In this and other series of which Dr. Elliott has knowledge, there have been 7 deaths, and the proportion of deaths to patients treated in Dr. Elliott's experience is somewhere between 1 in 200 and 1 in 300, with the proportion of toxic encephalopathies, followed by recovery, about the same.

In Dr. Elliott's opinion the Army and Navy would be justified in adopting some method of intensive arsenotherapy of early syphilis on a hospital basis (i.e., the ~~option~~, to be that of the medical officer in charge of a given hospital service, rather than of the patient).

Following Dr. Elliott, Dr. Hyman requested permission to speak briefly in an effort to reconcile the gross statistical differences between his own presentation and that of Dr. Webster, and felt that this was based on the fact that Dr. Webster had included as "unsatisfactory results" patients still seropositive when last seen, whereas Dr. Hyman had included these patients as "lost from observation."

It was finally brought out by a collation of the testimony of these observers and others that about 2300 patients have now been treated by the original five-day continuous intravenous drip method, or some modification of it; that there are at least 10 known deaths in this series, resulting from treatment; that at least 20 per cent, if not more, other patients have developed serious toxic reactions, usually toxic encephalopathies, followed by recovery; that the incidence of infectious relapse following this form of treatment is somewhere between 4 and 7 per cent, and that the incidence of "cure" is somewhere between 80 and 90 per cent.

This clinical evidence was followed by a presentation of laboratory studies by Passed Assistant Surgeon Harry Eagle, U. S. Public Health Service. Dr. Eagle has prepared for the subcommittee an abstract of his remarks, which appear herewith as Appendix "D".

Following Dr. Eagle's presentation there ensued a general discussion by the subcommittee of the intensive arsenotherapy of early syphilis. The members of the subcommittee were impressed with the high incidence of serious toxic reactions observed by this treatment, by the high death rate, which is somewhere between 1 in 200 and 1 in 300 patients treated, and by the admirable laboratory study of Dr. Eagle, which indicates that the optimum time-dose relationship is, as yet, unknown. Because of these considerations, the following motion was made, seconded, and passed, as a recommendation to the Surgeons General, U. S. Army and Navy:-

MOVED THAT THE INTENSIVE ARSENOTHERAPY OF EARLY SYPHILIS (INCLUDING THE SO CALLED FIVE-DAY TREATMENT) BE CONSIDERED AS STILL IN THE EXPERIMENTAL STAGE; THAT OPTIMUM TIME-DOSE RELATIONSHIP STILL REQUIRES TO BE ESTABLISHED BY FURTHER ANIMAL AND SUBSEQUENT CLINICAL EXPERIMENTATION; THAT AT PRESENT THE METHOD CANNOT BE RECOMMENDED FOR ROUTINE USE BY THE ARMED FORCES.

The Subcommittee then proceeded to a consideration of certain research projects. The project of Doctors Arthur Schoch and Lee Alexander of Dallas, Texas, for an evaluation of short term intensive arsenotherapy of early syphilis for ambulatory patients, was reconsidered at the request of the Committee on Chemotherapeutics and other Agents, and the Subcommittee on Venereal Diseases again voted to accept this project and to rate it "A". A copy of the letter to Dr. Perrin Long, Chairman of the Committee on Chemotherapeutics and Other Agents presenting the point of view of the Subcommittee is herewith appended as Appendix "E".

The application of Doctors Charles Carpenter and Stafford Warren of Rochester, New York, for a clinical study of combined fever therapy and chemotherapy of early syphilis in Glen County, Georgia, was rejected on the grounds that the number of patients proposed to be studied was too small to establish data as to toxicity, that provisions for the long term follow up of these patients were uncertain, and that fundamental laboratory data concerning the method were as yet unavailable.

The application of Doctors Charles Carpenter and Stafford Warren of Rochester, New York, for a study of the toxicity and therapeutic efficacy of mapharsen and neocarsphenamine at fever temperatures in experimental syphilis in

rabbits was, however, accepted and rated "A". The reasons justifying this action of the subcommittee appear in the forwarding letter addressed to Dr. Perrin Long, Chairman of the Committee on Chemotherapeutics and Other Agents, a copy of which is herewith appended as Appendix "F".

The Chairman of the Subcommittee reported that the application of Dr. Abraham Cantor had been rejected by a mail vote of the Subcommittee's members following the information of additional evidence of Dr. Cantor.

The Subcommittee next proceeded to a consideration of the memorandum on the laboratory diagnosis of lymphogranuloma venereum. It was pointed out that the recommendation contained in the original version of this memorandum to the effect that chick embryo antigen for the diagnosis of lymphogranuloma venereum could be obtained from the Virus Laboratory of the Army Medical School, was inapplicable at the moment, since a current batch of antigen from this source had proved, in the Johns Hopkins Hospital clinic, to be inert. With the necessary deletions the memorandum was approved by the Subcommittee for forwarding to the Surgeons General, U. S. Army and Navy, a copy of it being herewith appended as Appendix "G".

At the request of Dr. E. H. Cushing, Division of Medical Sciences, National Research Council, there was next considered a communication from Lieut. Commander J. A. Marsh, M.C. U. S. Navy, Retired, Central Prophylaxis Station, San Diego, California, to Major General James Magee, Surgeon General, U. S. Army. In this communication Lieut. Commander Marsh reported certain experiences with 0.25 per cent silver picrate jelly in the prophylaxis of gonorrhoea. The Subcommittee took cognizance of the data presented by Lieut. Commander Marsh, but made no recommendations other than to suggest that further data on the use of silver picrate in the prophylaxis of gonorrhoea be gathered.

At five P.M. the meeting of the Subcommittee was adjourned.

Respectfully submitted,

J. E. Moore, M.D., Chairman

Appendix A

To the Minutes of the Thirteenth Meeting of the Subcommittee on Venereal Diseases, National Research Council, January 13, 1942.

Notes of Dr. Harold Thomas Hyman

I have requested the convocation of this special meeting for the purpose of discussing the advantages and dangers that might be inherent in the introduction of five-day treatment of early syphilis in the armed forces of the army and navy.

The subject matter will be developed along the following lines:

- (1) The development of the method.
- (2) Its accomplishment.
- (3) Its dangers.
- (4) The relative advantages and disadvantages as compared with the best available, routine methods of arsenotherapy.
- (5) A rebuttal of the critical articles.

The next speaker, Dr. Bernard Kaplan of Sing Sing prison, will speak on his experiences in an institution with limited facilities. He will speak of technic and toxicology, but will not, at the present time, evaluate his therapeutic results since his material is almost wholly concerned with latent, neuro- and visceral lues.

The third speaker, Dr. Herbert Rattner of the Cook County Hospital in Chicago, will report his personal observations in the treatment of more than 300 patients with early syphilis.

Finally, you will be addressed by Dr. David Elliott of the United States Public Health Service. Dr. Elliott, under the aegis of his Surgeon General, Dr. Thomas Parran and Dr. R. A. Vonderlehr, organized and directed the Mid-West Conference, which has concerned itself with the wider application of five-day treatment in the various cooperating states and universities. You shall judge for yourselves with what administrative skill, accuracy and objectivity Dr. Elliott is proceeding. His great work is, as yet, in a state of flux, hence it is with some reluctance and with certain reservation that he speaks today. Nevertheless, I am of the opinion that his accomplishments thus far may be projected and anticipated in the light of our more pioneer findings.

THE DEVELOPMENT OF THE METHOD

Massive dose chemotherapy by the method of the intravenous drip was first introduced in the treatment of early syphilis in February, 1933. The clinical material then, as now, was limited to seronegative and seropositive primary syphilis, and early and late secondary syphilis. Parenthetically, this is for the most part the clinical material that will present itself in the present exigency.

The original treatment consisted of the administration of a total of 4 grams of neoarsphenamine, given by intravenous drip between the hours of 8 A.M. and 6 P.M. for five consecutive days. In the first experiment, 25 patients were treated. The early reports were made in 1934. The five year report was published in 1939. The therapeutic results with the drug were highly satisfactory, exceeding 90 per cent "cure". The toxicity, particularly referable to peripheral neuritis (35 per cent), was disturbing.

Due to factors beyond our control, active work was interrupted until 1938. At that time, Commissioner John L. Rice of the Department of Health of the City of New York, called together a distinguished committee to supervise a repetition of the previous investigation. An additional 86 patients were treated by the original technic. Work was again interrupted due to a death which occurred from toxic encephalopathy. After deliberation, it was decided to abandon the use of the drug but continue the method, using another arsenical, and napharsen or arsenoxide was substituted. In a probatory manner, the drug was employed in increasing doses, beginning with a total of 400 milligrams and running up to 1200 milligrams in the five days. With the smaller doses, infectious relapse occurred much too frequently. By the method of trial and error, it became obvious that the optimal dosage approximated 1200 milligrams in five days, or 240 milligrams daily.

With the optimal dosage of 1200 milligrams, 118 patients were treated in late 1939 and early 1940.

To insure the meticulous accuracy and objectivity of observation, patients were referred alternately, on discharge, to Dr. Bruce Webster at the New York Hospital or Dr. Evan Thomas at the Bellevue Hospital. These men continued the follow-up observation. In each instance, patients were carefully examined by clinical methods. Blood and spinal fluid specimens were collected in triplicate. One serological examination was performed at the home institution; a second was sent to Mr. John Koopman of the New York City Department of Health; the third to Dr. John Mahoney. Blood specimens were tested by the Kahn and Kline methods. Mr. Koopman did a special Wassermann titration that read from 0 to 15+. Dr. Mahoney performed the standard Kolmer technic with readings from 00000 to 44444.

None of the patients received adjuvant treatment with bismuth, mercury, or hyperpyrexia. This was not due to lack of confidence in these modalities, but rather to the attempt to execute a relatively uncomplicated, clinical experiment from a pharmacological standpoint.

Previous publications have dealt with the results in the group as a whole. They included the data obtained with (a) neocarsphenamine and its higher toxicity; and (b) mapharsen in the lower dosage with the less favorable therapeutic results.

Today, I elect to discuss only the toxicity and immediate results in the 118 patients who received the 1200 milligram dosage. What transpired in the remainder of the group will be used as a background and as a possible indicator for the more prolonged follow-up observation.

Completion of Therapy

One hundred per cent of the patients completed therapy. It may be assumed, therefore, that the immediate toxicology has been recognized and reported.

Lost from Observation

Of the 118 patients, 18 (17 per cent) disappeared from observation immediately after the completion of treatment. Their "chance for cure" is identical with that in the followed group.

By contrast, case loss in 5 excellent clinics of the United States using routine conservative methods, approximated 84 per cent. In the United States as a whole, Dr. Russell approximates "case loss" at 95 per cent. With lapse from treatment by routine conservative methods, the patient has been incompletely treated. He has not the same "chance for cure" as those who have received adequate therapy.

Additionally, the toxicology in the lost group is unknown. Indeed, it is not unlikely that the lapse from treatment was occasioned by untoward and unfortunate treatment sequelae. Syphilologists agree that the inadequately treated patient is more apt, than his untreated fellow, to develop the late, visceral manifestations of the disease, particularly neurosyphilis.

Completed Records

Subtracting our lost from the whole number of patients, 100 (85 per cent) of those who completed therapy present relatively adequate records at the present time. This is to be compared with the records published by those who advocate routine conservative therapy. Thus, in the recent excellent review by Padgett, at the end of five years (a minimal period), 551 patients are reported from an original group of 6000. These records are based on 9 per cent of those who initiated treatment. The fate of the remaining 91 per cent is not recorded.

Span of Observation

The present group was treated 18 to 24 months ago. Some of them have not been seen for several months due to the shifting of population at the present time. However, we have their social security numbers and should shortly fill in gaps as patients are re-located, maintaining our prolonged follow-up at about 85 per cent.

To anticipate criticisms of the relatively short span of observation in this group receiving optimal dosage, we call attention to the fact that in the 1933 group, now in the eighth year and the small dose mapharsen group now in the fourth year, experienced no significant change in the second, third, or fourth years of observation. When infectious relapse, which accounted for 90 per cent of our failures, was encountered, it commonly occurred at a critical period between the tenth and the eighteenth weeks. It seems reasonable to prognosticate that few significant changes will occur in the later observation of the present group of patients.

Retreatment

Whereas originally we planned to stand or fall on a single course of

treatment, the incidence of 8 per cent infectious relapse (to be compared with 12 per cent by routine conservative treatment (Moore -- page 23), led us to a policy of retreatment by the original method with the original dose. This was carried out in 6 or 6 per cent of the 100 followed cases. Parenthetically, there was no unusual toxicology or sensitization in the retreated group.

There are, therefore, 100 followed patients, 6 of whom were retreated. In other words, there are 106 treatments for 100 patients.

Failures

There are 4 irrevocable failures (4 per cent). Three of the patients were not retreated, and hence are failures of a single course. The fourth patient was retreated and is a failure the second time.

The manifestations of failure were limited to infectious relapse and Wassermann fastness. There were no clinical evidences of visceral syphilis. All spinal fluids were normal.

Pending

Four patients (4 per cent) are in the pending group. These men are clinically well, but their serology has not yet completely cleared. They would correspond to what Dr. Moore classifies as S.T.S.

To illustrate the progress of these patients, the serologies are undernoted.

Two patients pend, after a single treatment course. One of these (#233) originally had a Kolmer titration of 44444 and a Koopman figure of 7. At the present time, the kolmer is 22222 and the Koopman is negative.

Patient number 245 originally was Kolmer 44444 and Koopman 6. At present the Kolmer is 1+000 and the Koopman is 1.

Two of the retreated patients have proceeded even further in their serology. Thus number 153 originally was Kolmer 44444 and Koopman 6. The serology is now Kolmer @ 0000 and Koopman 0. The other of the retreated cases (#204) was originally Kolmer 44444 and Koopman 7. At the present time the Kolmer is 1+000 and Koopman 1.

Despite the fact that three of these four pending cases have almost completely negatived their serological findings, we do not, as a matter of policy, include as satisfactory any individual who has any serological findings other than zero on several examinations.

Satisfactory Results

The remaining 92 patients (92 per cent) are completely satisfactory re

sults at the present time. They have no clinical evidences of syphilis. The precipitation and complement-fixation tests are negative. Some of the men have not been seen for several months, but no one is included in this group who did not have several negative tests. We confidently expect to have more complete data as time progresses.

Summary

Employing 1200 milligrams of mapharsen over a five-day period in the treatment of early syphilis, we report, at the present time, favorable results in 96 per cent. Only one patient has a significant amount of reagin in the blood.

SPINAL FLUID EXAMINATION

There are 71 spinal fluid examinations. Each is normal. Because of the relatively short span of observation, this finding necessitates support from the findings in patients who have been observed for a longer period of time. Exclusive of the present group, there are 268 patients that have been treated by us. There are additionally 236 spinal fluids, or a total of 307 in all. Three hundred six of the total are and have been completely normal. One spinal fluid, in all our experience, has been positive. That single exception occurred in a merphinst who, at the time, had a wife who suffered from infectious syphilis.

Neurosyphilis

There has never been a patient treated by us who showed clinical evidences of neurosyphilis.

Cardiovascular syphilis

There has never been a patient treated by us who showed clinical evidences of cardiovascular syphilis. Teleroentgenograms were done on the majority of the patients.

Other Evidences of Visceral Syphilis

Except for the infectious relapse, there has never been a clinical manifestation of syphilis in any of our patients.

Reinfection

There have been at least 12 instances of reinfection in the total series. For the most part, we have reported these as infectious relapses in order that our statistics might appear in their worst possible light. Thus, in this large dose mapharsen series, at least three of the men reported as infectious relapses, in all probability had reinfection. Rather than quibble, we accepted the patients as infectious relapses and retreated two. One we accepted as a failure, though there is good clinical reason to believe that the man had more likely a reinfection and hence was a successful therapeutic result.

The Comparative Accomplishments by the Best Available Routine, Conservative Method.

Beyond their absolute value in evaluating the efficacy of five-day treatment, the figures above noted are to be compared with the accomplishment by the best available routine conservative methods.

Concerning this, Dr. Moore states (page 44) "The chance for cure by the best available methods of conservative treatment in early syphilis is a 100 per cent probability of biologic cure in seronegative primary syphilis, 80 to 90 per cent in seropositive primary syphilis, 80 to 95 per cent in early secondary syphilis." Best available methods of treatment, according to Dr. Moore's definition are the continuous and continued therapy.

The figures which we have presented closely approximate Dr. Moore's stated "chance for cure." However, the published reports of best available conservative therapy do not seem to fulfill Dr. Moore's optimistic prognostication. Thus, Dr. Padget, reporting on 551 patients, followed for five years or more, and chosen from an original group of approximately 6000 (9 per cent of those who initiated treatment), shows that 65.7 per cent were "cured"; 14.9 per cent were clinically well but had positive serology (S.T.S.). Thus, the Padget figure of 65.7 per cent compared with our figure of 92 per cent. The addition of Dr. Padget's cured and S.T.S. group give 80.6 per cent satisfactory, compared to our 96 per cent.

Recall again that we are reporting on 83 per cent of the total number of patients treated, while Dr. Padget has records of but 9 per cent. Recall also that, of our lost patients, each had completed therapy and had the same chance for cure as the followed group, whereas in the Padget group there is no such assurance for the lapsed 91 per cent.

On the other hand, Dr. Padget has observed his group for five years or more, whereas our present group ranges between 18 and 24 months.

The accomplishment of intravenous drip arsenotherapy by our method is not alone on the positive side of the ledger. It will be recalled that we report complete freedom from clinical manifestations of late syphilis. Compared to this, Dr. Padget had 3.8 per cent of benign late syphilis; 4.5 per cent of cardiovascular syphilis; 12.3 per cent of syphilis of the central nervous system; 1.3 per cent of multiple late syphilis. Of these complications that incapacitate patients, force them to seek entrance in the chronic disease hospital and would add to your pension costs and disability payments, we had none.

Again in the Padget series, 10 patients (1.8 per cent) die of their syphilis. We have never had a single patient succumb to the infection. Recall again that the Padget mortality is limited to the small percentage of patients that have been followed. What indeed must be the syphilis mortality in the 91 per cent of the 6000 patients whose records are incomplete?

Again our critics will point out that there has not been sufficient time for our patients to have developed these disabilities. To this we respond that the neocarsphenamine group and the small dose napharsen group have been studied in excess

of 3 years. Dr. Vonderlehr reports that there is no significant difference in the incidence of satisfactory results in patients followed 3 to 10 years and those from 10 to 20 years.

Shortly, we shall discuss the problem of treatment death. When we do so, we ask you to remember in the Padget group, for example, that 1.8 per cent died of syphilis and approximately 20 per cent suffered from the visceral manifestations of the infection.

Seronegative Primary Syphilis.

This section on accomplishment will close with the problem that probably concerns you most, namely, the treatment of primary seronegative syphilis. By all methods and with all dosage, we have treated 46 such patients and 46 were "cured". The 12 that were given neocarsphenamine and the 16 with the 1200 milligram dosage of napharsen proceeded without difficulty to complete seronegativity. The remaining 18, that had the smaller dosage of napharsen, included 2 who require retreatment since they had less than optimal dosage the first time. Both these men cleared by the second treatment, thus achieving a practical accomplishment of what Dr. Moore indicates in his table on probabilities.

THE TOXICITY AND DANGERS INHERENT IN FIVE-DAY TREATMENT

The dangers inherent in arsenotherapy include minor reaction, major disturbances, and treatment death.

Minor Reactions

The minor reactions experienced in intensive treatment include gastro-intestinal distress, primary and secondary fevers, toxicodermata, transitory jaundice, and albuminuria. These phenomena have "nuisance value" and need not concern us today.

Major Disturbances

The major disturbances incidental to arsenotherapy include toxic hepatitis, blood dyscrasias, renal disturbances, dermatitis exfoliativa, and the toxic neuropathies.

Of the liver, kidney, skin, and blood complications, we have personally experienced none in the napharsen series and one dermatitis exfoliativa with recovery in the neocarsphenamine group.

The toxic difficulties relative to intensive therapy are wholly concerned with the neuropathies. In the neocarsphenamine work, we had 35 per cent of peripheral neuritis, much of it moderate or more than that in severity. With napharsen, we have reduced that to 1.7 per cent of exceedingly mild intensity. That problem seems to be solved.

At this time, we may digress to inquire into the reason for the lesser toxicity of napharsen. Our belief is that it is simply a matter of arsenic content.

According to our clinical observation, the optimal therapeutic dose of neocarsphena- mine is 4 grams compared to 1200 milligrams of mapharsen. The reason for the lesser toxicity of the arsenoxide, we believe, is the fact that 4 grams of neocarsphena- mine contains approximately 800 milligrams of arsenic, while 1200 milligrams of mapharsen contains approximately 360 milligrams or less than half.

The single problem in toxicology that we have not overcome is that known as hemorrhagic encephalitis or perhaps better, toxic encephalopathy. We encountered this complication approximately once in each hundred cases, and while we ourselves have not had a treatment death in the mapharsen series of 276, Dr. Elliott will shortly report an incidence of fatal encephalopathy approximating 0.5 per cent.

We who advocate the use of intensive treatment by the five-day method, must straightforwardly and directly accept, against our accomplishment, a probable incidence of mild, moderate, or severe encephalopathy resulting from treatment, once in a hundred times, and a treatment death once in two hundred to three hundred times.

Let us with equal candor inquire into two questions. (1) Are the toxic encephalopathies a manifestation of overdosage or idiosyncrasy? (2) How commonly does toxic encephalopathy occur by routine conservative methods?

I believe that the toxic encephalopathies are manifestations of idiosyn- crasy and not overdosage. I base this on two clinical observations. The first of these is the fact that with routine, conservative treatment (as in the Cole series) the complication commonly occurred after the third or fourth injection of the us- ual routine dose. The second reason, as you will shortly see from Dr. Kaplan's report, is the absence of this complication in his series of individuals with late syphilis, suggesting the possibility that the "reactors" have been eliminated by a process of natural selection.

If the hypothesis of idiosyncrasy is correct, encephalopathy is not a mani- festation of overdosage. It should be as commonly encountered in routine as in massive dose arsenotherapy. Whether or not this is so is the problem that we must next consider.

I have previously pointed out the large percentage of case loss by routine, conservative methods. I have previously indicated that there is a possibility that the patient who lapses from treatment does so for the very reason that he is a "reactor". Under these circumstances, the followed group would be weighted with those who do well and the lapsed group with those who have treatment difficul- ties.

With a syndrome such as encephalopathy which may come on hours or days after the injection, and which may be manifested by headache, disorientation, coma, or convulsion, what should be more natural than that the patient should discontinue treatment if he interpreted his disturbances as the result of the injection? If the disturbances were of more than moderate severity and he became comatose or experienced convulsions, would he be returned to the ambulatory syphilis clinic? Would the neighborhood doctor recognize the syndrome and report it to the syphilol- ogist? If the patient were taken by ambulance to a general hospital, how likely is it that the diagnosis would be made, and if made, called to the attention of the

treatment group?

That these speculations are not idle is suggested by the discrepancy that exists in the reports of the most reputable and informed syphilologists. Thus, Dr. Moore in the Journal of the American Medical Association stated that our incidence of this complication was 1500 times greater than his. Later, in his current text (page 583) he has amended that statement to "225 times as great". Hahn, reporting from Dr. Moore's clinic, in a current issue of the American Journal of Syphilis, Gonorrhoea, and Venereal Diseases (page 683) says: "The case incidence of hemorrhagic encephalitis with massive dose arsenotherapy is 60 to 70 times that of routine therapy." This, the comparative range in this one group extends between 60 to 1500 times.

In the Cole series to which we have made previous reference, there were 6 deaths from toxic encephalopathy in 1212 patients treated. This is an incidence of 1 in 200, about equal to ours. Hahn quoted above, remonstrated with us for using this comparison, since 4 of the 6 deaths occurred with sulfarsphenamine. However, that still leaves 2 encephalitis deaths in 1160 patients treated with arsphenamine or neoarsphenamine. This fatal incidence is approximately 1 in 550. Since we have 2 or 3 non-fatal cases to each death, Dr. Cole's incidence with neoarsphenamine and arsphenamine must just about equal ours. Surely Dr. Hahn cannot be referring to this series when he states that our incidence of hemorrhagic encephalitis is 60 to 70 times that of routine therapy.

Perhaps it is this type of dilemma that leads Dr. Hahn to state in his summary (page 681) "The only long-term modern statistics concerning the mortality rate of antisyphilitic treatment are those of the United States Navy. Reliable data on the incidence of hemorrhagic encephalitis are not available," and again (page 660) "The Cooperative Clinical Group study gives no useful information concerning total mortality rate or actual incidence of hemorrhagic encephalitis, for the obvious reason that it was planned to include only patients under treatment for at least six months. As will be shown subsequently, fatal reactions tend to occur during the first six months of therapy." On the next page (661) he adds, "Especially inaccurate are the published and quoted data of the incidence of hemorrhagic encephalitis."

Treatment Deaths

Employing mapharsen, we have never personally had a treatment death. This we are convinced is a matter of pure good fortune. We freely admit that, by our method, a fatal sequellum may be anticipated once in every 200, 300, or 400, patients. Since the sole cause for death in our series has been toxic encephalopathy, what has been said above is also relative to "treatment deaths" so far as we are concerned. But this is not true of other serious treatment complications, absent from our series, but encountered in routine conservative treatment. Dr. Moore gives the incidence of dermatitis exfoliativa as 1 to 126 with arsphenamine, 1 to 197 with neoarsphenamine; of hepatitis, 1 to 117 for arsphenamine, 1 to 282 with neoarsphenamine and additionally described thrombocytopenia, granulocytopenia, and aplastic anemia, all of which have known mortality. These complications must cause some mortality as apparently recognized by Dr. Hahn, who estimates our incidence of hemorrhagic encephalitis as 60 times routine conservative treatment and our mortal-

ity incidence as 3 to 7 times. He states that the Johns Hopkins treatment deaths were 1 to 1250, but again we point out that this estimation which is based on conservative cases, is computed from the records of that small percentage who have been followed.

The Risks Summarized

The risks of 5 day treatment incidental to grave morbidity and mortality resulting from (a) treatment and (b) the ravages of syphilis may be succinctly summarized.

With our methods:

- (1) No death from syphilis has occurred.
- (2) No visceral manifestation of syphilis has occurred.
- (3) The treatment risks consist of 1 to 100 toxic encephalopathy and 1 to 200 or 1 to 300 treatment deaths due to toxic encephalopathy.

Against this, as we view it, the risks of routine conservative treatment may thus be summarized.

- (1) Death from syphilis 1.8 per cent of the followed cases (Padgett). Death from syphilis in lapsed patients unknown.
- (2) Visceral damage from syphilis approximately 20 per cent in followed cases. (Padgett). Visceral damage from syphilis in lapsed group unknown, but admittedly higher.
- (3) Dermatitis exfoliativa, 1 to 126, 1 to 197 (Moore)
- (4) Hepatitis, 1 to 117, 1 to 182 (Moore).
- (5) Blood dyscrasias?
- (6) Toxic encephalopathy. "Many times". (Schanberg); 1 to 200 to 1 to 550 fatal cases (Cole), 2 in 27, 400 patients (Moore); United States Navy, 1 in 77, 784 injections; Stokes, 1 in 99, 600 injections.
- (7) Treatment deaths, 12 in 1212 (1/100) (Cole); 1 to 1,250 (Hahn and Moore); United States Navy, 1 to 29, 868 injections; Stokes, 1 to 21,000 injections.

THE ADMINISTRATIVE AND ECONOMIC ASPECT OF SYPHILOTHERAPY

The introduction of five-day treatment in the army and navy would have the following implications relative to administrative and economic aspects:

- (1) The patient would be hospitalized for approximately eight days.
- (2) Except for perhaps 6 per cent of the men who would require retreatment for infectious relapse, no other therapy need be administered.

(3) Except for reporting at weekly intervals for the first four months and monthly intervals thereafter, no other observation or care would be necessitated.

(4) There should be no significant incidence of clinical syphilis. There should be no significant post-war hospitalization, disability, pension payments or death benefits in the treated group.

(5) The total of man days lost in treatment should be reduced by perhaps 70 or 80 per cent.

(6) The administrative work and organizational disruption due to the necessity of repeated weekly injections over the course of eighteen months is reduced to a minimum.

REBUTTAL OF CRITICISMS PARTICULARLY THOSE REFERABLE TO LABORATORY WORK

A persistent criticism of our investigation has been the lack of preliminary work on laboratory animals. Thus Dr. Moore states (586) "It is unfortunate that fundamental laboratory data relative to five-day treatment was not accumulated before the method was tried clinically."

To this, I desire now for the first time to make a public reply.

I have been a pharmacologist for the past twenty-three years. I have convinced myself that animal pharmacology differs widely from human pharmacology. The touchstone of clinical therapy is the result on man himself. This is particularly true of the chemotherapy of infection. Each biologist will agree that experimental inoculation of animals followed by treatment presents a much different problem than natural infection, as experienced by the living organism. The most recent example of this exists with the drug Promin. This substance is signally successful in the treatment of experimental tuberculosis in guinea pigs. In the human, my recent work proves it to be valueless. These findings are confirmed elsewhere. My earlier work which led to the discovery of speed shock, was concerned with the "cure" of malignancies in the mouse with doses of melanin. Clinically we may as well have injected distilled water. I am convinced that fundamental laboratory work on clinical chemotherapy must be done sooner or later on man himself. Laboratory work may or may not be helpful. In this instance, I elected to go to the clinic itself. Here we employed every safeguard. In addition to the usual routine examination and care as provided in every first-class hospital, we did daily blood counts including platelets, before and after treatment, blood chemistry and renal function tests, liver function tests, arsenic excretion studies in urine and stool and arsenic concentration in blood. We did not sacrifice any patients, at stated intervals, to make arsenic determinations on tissue, but other than that I know of no error of omission.

This accomplishment is to be compared to what is known relative to routine conservative treatment. Where are there studies comparable to ours? How was the time-dose relationship worked out in continuous and continued treatment? Why 0.4 gram of arsphenamine? Why 60 milligrams of napharsen? Why weekly intervals?

Why 20 doses per series? Why 70 injections total? Why (page 585) a theoretical blood arsenic level for routine conservative treatment to be compared with our factual graphs?

Have not our critics - like us - arrived at their systems by the methods of trial and error, which is in the end the critical-clinical method? Have they not criticized us for scientific derelictions, when they themselves with greater facilities, longer years of study, failed to show data and statistics equal to ours?

But let us return to the laboratory work. Dr. Moore states, with reference to the recent work on the toxicity of arsenic for rabbits, that these results "are applicable to human beings." With this principle I am in disagreement. Concerning this point, I quote my chief, Professor Charles C. Lieb who writes, "Moore states that there is no good reason to doubt that the minimal lethal dose found in lower animals (dog and rabbit) also is the minimum lethal dose for

man. This I think a most dangerous assumption, and it is not justified." But let us not tarry longer with this academic discussion concerning the relationship of animal experimentation to human therapy. Let us for the moment accept the fact that Dr. Moore is correct in stating that the results in the animals are applicable to human beings, and in this light take up the published findings of Magnuson and Raulston, to which Dr. Moore refers.

Relative to the Therapeutic Index.

Magnuson and Raulston state "the dose of napharsen which has been used in the continuous drip treatment of syphilis approximates 4 milligrams per kilo per day for a five-day period, while the maximum tolerated dose in dogs by the continuous drip is 10 milligrams per kilo per day, giving a ratio of 2.5". Dr. Moore has been more generous to us, since he states (page 537), "The Treatment schedule most frequently used by the intravenous drip is only one-third the dose which kills half the animals."

Dr. Moore then goes on to say that this therapeutic index of 1 to 3 is "dangerously close to the toxic levels."

With this conclusion I take issue. If the therapeutic index is regarded as 1 to 3, then there is a factor of safety in our method between 1200 milligrams and 3000 or 3600 milligrams, quite ample for all clinical purposes. Commenting on this, Dr. Lieb states, "A drug with a factor of safety of 3 (determined by comparing the effective therapeutic and minimal lethal dose on the same species) is not perfectly safe but it is relatively safe. For example, phenobarbital and sodium barbital tested on dogs, have each a factor of safety of only 1.5. Surely if we could transfer results from animals directly to man (as Moore proposes), neither of these useful drugs could be justifiably employed in practice."

As to Intravenous Drip Versus Multiple Injections

The second point of attack on our work has been relative to the comparison of the intravenous drip and multiple injection. Concerning this point, there are both clinical and laboratory data.

Clinically, Dr. Thomas has published carefully compiled data on the two methods. From his work, he concluded "The continuous drip has no special therapeutic advantages over intensive treatment by multiple injection." As I wrote Dr. Thomas on July 7th, I believe that his figures are not in accordance with his conclusions. Thus, he had to fall back in his dosage from 1200 milligrams to 840 milligrams and 540 milligrams. The span of treatment was increased from 5 days to 8 days. In order to make up for the lessened efficacy of arsenotherapy, other variables were included such as typhoid vaccine injections and hyperpyrexia.

In Dr. Thomas's analysis of the clinical results, he included in the satisfactory group those who were almost seronegative. You have seen how scrupulous we have been to exclude from the favorable group any patient with the slightest possible reagin in the blood. When our criteria are applied to Dr. Thomas's group, as reported recently, the favorable results fall to 76.8 per cent as against our figure that is in excess of 90 per cent.

Relative to toxicity by the two methods, Dr. Moore (583) himself points out that the incidence of hemorrhagic encephalitis is higher in the Thomas series than in our series, and this despite the fact that his dose was lower.

Magnuson and Raulston have compiled experimental data on this point. From their experiments, they concluded:

(1) "It evidently makes no difference whether the drug is given slowly and continuously over a twelve-hour period or in three single large doses during the same time interval. The net effect is the same in either case."

From this conclusion, one would judge that intravenous drip method has little to recommend it. If you will bear with me another moment, I shall analyze the data on which this erroneous conclusion was based.

The authors studied arsenic excretion in urine and stool; arsenic retention in tissues and arsenic concentration in the blood. Obviously, the desideratum would be adequate arsenic excretion by urine and stool, maintenance of an effectual blood concentration, and minimal tissue retention in order to avoid toxicity.

As to the comparative arsenic excretion, the authors state, "It may be seen that the figures (of multiple injections) do not present the sharp differentiation between those animals that live and those that died, such as was encountered in those that received continuous drip. Furthermore, the total excretion was almost always less than that found in the previous group (drip). The average total excretion dropped from 42.2 per cent in the first group (intravenous drip) to 28.4 per cent in the present group (multiple injection). This difference was most marked in the urinary excretion, which averaged 35.6 per cent of the arsenic administered with the continuous drip but only 16 per cent of that given by interrupted dose."

Is it not fair to conclude that relative to arsenic excretion in urine and stool that the continuous drip method excels that of multiple injection?

Nor is that all, since the authors in explaining the differences in excretion state: "With the continuous drip, the animals were receiving approximately 600 c.c. of intravenous fluid each day, and in addition were drinking water as desired. With the interrupted doses, the fluid intake was dependent upon the thirst of the animal which was very irregular. Many of the animals were nauseated and refused to drink."

Certainly this statement needs no amplification from me.

As to blood arsenic concentration, the authors present two graphs that are comparable. These are concerned with the changes that result from dosages of 10 milligrams per kilo per day, given first by drip and later by multiple injection.

I shall pass these curves around for your examination. You will note in the intravenous drip curve that four graphs are closely parallel. They reach a concentration approximating 100 micrograms on the first day, 125 on the second day, 150 on the third and fourth days, and 175 on the last day. Those of you who are familiar with our clinical studies, as done by Dr. Sobotka, will recall that the curves presented by us as they appeared in the human patient, were almost identical with those of the experimental animal. The blood levels were lower since we gave smaller doses, but the graph was a replica of those prepared by Dr. Magnuson and Dr. Raulston.

Compared to this, by the multiple injection method, there is no such regularity. One animal reached a concentration of 500 micrograms on the first day. That animal died, so the high concentration undoubtedly contributed to, if it did not cause, the fatality. Of the remaining three animals, two never reached a concentration of 100 micrograms at any time, the third touched a 100 microgram level twice during the course of treatment and seems to have reached a level of about 150 micrograms at the last analysis.

Is it not fair to conclude from this that by intravenous drip a relatively constant and even arsenic concentration is achieved and maintained during the period of therapy? Whereas with the multiple injection method the results are irregular, the single high concentration produced a fatality and the low concentrations could not have had the therapeutic efficacy of the level obtained by the drip.

Finally, the authors have remarkably accurate data on tissue retention. I shall not go into their method of calculating the estimated mapharsen retention in milligrams per kilo per day, but I shall call attention to the importance of this calculation, since those animals whose retention was less than 7 milligrams in the longer study and 8 milligrams in the shorter study, universally survived, whereas those whose retention exceeded 7 milligrams in the 5 day study and 8 milligrams in the 2 day study presented a high mortality rate irrespective of dosage.

It would seem to be a fair conclusion that excessive tissue retention was related to toxicity and mortality. With this in mind, observe that in each instance an arsenic retention of less than 7 milligrams occurred in 50 per cent of those

treated by drip and but 13 per cent of those treated by multiple injection.

The experimental studies of Magnuson and Raulston seem to prove, according to our viewpoint:

(1) The factor of safety of 2.5 or 3 to 1 (as determined by comparing the effective therapeutic and the minimal lethal dose) is relatively safe, to use Dr. Lieb's phrase.

(2) The method of the intravenous drip exceeds in safety that of multiple injection, since there is a greater arsenic excretion by urine and stool, lesser subjective symptomatology, a lessened tissue retention, and an absence of overwhelming arsenic concentration, such as might prove toxic and cause a sustained arsenic concentration to assist the therapeutic result.

Thus the researches of Drs. Magnuson and Raulston, if they are acceptable to Dr. Moore, demonstrate the irregularity and toxicity of rapid injection. They support the concept of speed shock, as enunciated by me ten years ago. They prove the relative innocuousness of the slow intravenous drip.

These considerations impel us to offer for your approval the possibility of introducing intravenous drip arsenotherapy for early syphilis in the armed forces. The method promises greater than a 90 per cent curability. It has a definitive treatment risk approximating 0.5 per cent. There should be no repercussions in the nature of late sequelae, significant manifestations of the infection or late visceral damage. There need be but a small percentage of retreatment by the original method, no other form of therapy, no interruption of routine, no further man-day loss to your organizations, no later threat of a mass of chronic hospitalization due to ancient lues, no disability or pension.

Appendix B

To Minutes of the Thirteenth Meeting of the Subcommittee on
Venereal Diseases, National Research Council

Data regarding the intensive arsenotherapy of late syphilis
supplied by Dr. Bernard Kaplan, Sing Sing Prison Hospital

Ossining, New York.

Total number of patients who received intensive anti-luetic therapy:- 258
Retreated: 21

Diagnosis in patients receiving above treatment:-

Asymptomatic central nervous system syphilis.....	60
Symptomatic central nervous system syphilis.....	20
Late latent syphilis.....	127
Early latent syphilis.....	40
Cardiovascular syphilis.....	5
Primary and secondary syphilis.....	4
Congenital syphilis.....	2

Type of treatment course employed:

5 day mapharsen drip	142
Mapharsen drip (other than 5 days)	16
Mapharsen drip and typhoid vaccine intravenously..	94
Mapharsen drip following malaria.....	13
Multiple syringe technique.....	14

Total amount of arsenic employed in each of 279 courses of treatment:

Less than 1000 milligrams.....	41
1000 to 1200 milligrams.....	118
1201 to 1400 milligrams.....	65
1401 to 1600 milligrams.....	55

Some amount of previous antiluetic therapy had been received by approximately 50% of the 258 patients.

Toxicology: No instances of blood dyscrasia, hepatitis, exfoliative dermatitis, renal damage, hemorrhagic encephalitis, and no fatality. Minor symptoms, such as nausea and vomiting, headache and dizziness and arm pain, approximately 50 to 75%. Peripheral neuritis 7%, toxicoderma 5%; primary and secondary fever 28%.

Appendix C

To the Minutes of the Thirteenth Meeting of the Subcommittee on
Venereal Diseases, National Research Council

Data supplied by Dr. Even Thomas, Bellevue Hospital, New York,

as to intensive arsenotherapy of early syphilis.

Number of Treatment Courses from Dec. 1939 to Jan. 1, 1941.

Number of patients treated	654
Retreatments	<u>40</u>
Total number of treatment courses	694

Distribution of Cases by Type of Treatment

Total number of treatment courses	694
Treated with napharsen only	280
Treated with napharsen and typhoid vaccine	413
Treated with napharsen and artificial fever	1

Distribution of Treatment Courses with Napharsen Only by Stage of Disease

Total number	280
Primary and secondary syphilis	273
Latent and others	7

Reactions

Cerebral Reactions with Napharsen Only

	<u>Number</u>	<u>Per cent</u>
Treatment Courses	280	100
Cerebral reactions (total)	<u>3</u>	<u>1.07</u>
Total fatality due to hemorrhagic encephalitis (treated with 0.9 gms. napharsen)	1	.36
Recovered after hemorrhagic encephalitis (treated with 0.99 gms. napharsen)	1	.36
Mild reaction (few convulsions) (treated with 0.77 gms. napharsen)	1	.36

In this group, 1 patient with no cerebral reactions
had marked spinal fluid change.

Cerebral Reactions with Mapharson and Typhoid

	<u>Number</u>	<u>Per cent</u>
Treatment Courses	414	100.0
Cerebral reactions (total)	<u>4</u>	<u>.96</u>
Fatality due to an encephalopathy (exact etiology unknown) (treated with 0.84 gms. mapharson and 2 fevers)	1	.24
Mild reactions (treated with 0.41 to 0.7 gms. mapharson and fever)	3	.72

In this group, 7 patients with no cerebral reactions had marked spinal fluid changes.

Treatment of Early Syphilis
(Primary and Secondary Syphilis)

Status of 151 Cases, 8 to 24 Months after Treatment with 0.9 gm. to 1.2 gm. Mapharson

	<u>Number</u>	<u>Per cent</u>
Cases treated	151	100.0
* Lost	65	43.05
Followed	86	56.95
Status of 86 cases followed		
Probable favorable results	71	82.6
Now seronegative (68 cases)		
** Almost seronegative (3 cases)		
Still seropositive	4	4.7
Relapse or reinfection	<u>11</u>	<u>12.7</u>
Total	86	100.0

* Of the 65 lost cases, 24 were seronegative when last seen, 19 of these having been followed 9 to 17 months after treatment.

Status of 122 Cases, 8 to 14 Months after Treatment with 0.66 gm. to .84 gm. Mapharson

	<u>Number</u>	<u>P.r cent</u>
Cases treated	122	100.0
* Lost	46	37.7
Followed	76	62.3
Status of 76 cases followed, probable favorable results	53	69.7
Now seronegative (50 cases)		
Almost seronegative (3 cases)		
Still seropositive	4	5.3
Relapse or reinfection	<u>19</u>	<u>25.0</u>
Total	76	100.0

* Of the lost cases 9 were seronegative when last seen, 5 of these having been followed 8 to 12 months after treatment.

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** By almost seronegative, we mean cases whose serological tests are completely negative except for a doubtfully positive State titer.

Those listed as still positive have State titers which are falling and may become negative in time.

Status of 120 Cases, 8 to 13 Months after Treatment with 0.54 gm. to 0.6 gm. Mapharsen and 3 to 4 Fevers induced by Typhoid Vaccine.

	Number	Per cent
Cases treated	120	100.0
Lost	47	39.2
Followed	73	60.8

Status of 73 cases followed, probable favorable results

	63	86.3
Now seronegative (56 cases)		
Almost seronegative (7 cases)		
Still seropositive	1	1.4
Relapse or reinfection	<u>9</u>	<u>12.3</u>
Total	73	100.0

Spinal Fluid Examinations 6 to 24 Months after Treatment

Total number examined	203
Negative spinal fluids	201
Spinal fluid 12 months after treatment showing 10 cells but otherwise normal. (Blood Wassermann negative)	1
* Spinal fluid 7 months after treatment showing a positive Wassermann and 5 cells; globulin, total protein, and colloidal gold tests normal.	1

* This case was relapsing secondary syphilis with a strongly positive spinal fluid before treatment. Seven months after treatment her spinal fluid is inactive except for 5 cells and a positive Wassermann test. Her State blood Wassermann titer is steadily falling.

Appendix "D" to Minutes of 13th Meeting of the Sub-
Committee on Venereal Diseases, National Research Council

Statement of Passed Assistant Surgeon Harry Eagle, U. S. Public Health Service

An Experimental Evaluation of the Intravenous Drip and Other
Intensive Methods for the Treatment of Syphilis.

The report that early syphilis may be effectively treated, and in most cases definitively cured, within five days by administering neocarsphenamine or mapharsen in an intravenous drip, is of obvious importance both to the individual patient and to the current control program. This intensive procedure is, however, many times more dangerous than standard clinic practice, causing death in 0.3 to 0.5 per cent of the cases, and serious toxic reactions in approximately one of every hundred patients treated. Under these circumstances, its utility as a routine procedure is debatable.

A study on the toxicity and chemotherapeutic efficacy of the intravenous drip applied to the treatment of rabbit syphilis was begun in the fall of 1939. It was hoped that the data would provide information, not available from the human experiment, as to the margin of safety afforded by this procedure. As the study progressed, its scope was enlarged to include other intensive methods, as well as more conservative procedures, and an attempt was made to provide as wide a variation in the time-dose relationship as was feasible experimentally.

To date, approximately 2,000 animals have been used in the study, and 10 different treatment schedules have been evaluated. For each of these schedules, both the toxicity and the therapeutic activity have been determined, using 6 to 12 rabbits at each of 4 to 6 dosage levels. "Mapharsen" (3-amino-4-hydroxy phenylarsine oxide) was used throughout. To summarize the results in brief, the five-day intravenous drip and, indeed, any similar intensive schedule over so short a period, provides a dangerously narrow margin of safety as compared with the traditional weekly injections over a period of 12 to 18 months. Treatment may, however, be intensified safely along more conservative lines. Thus, injections three times weekly for 4 to 6 weeks provide a margin of safety comparable with that afforded by 20 to 30 weekly injections. With all necessary reservations, there is reason to believe that these data may be of significance for the treatment of the human disease.

Arranged in the order of decreasing intensity, i.e., increasing total duration of treatment, the ten experimental schedules were as follows:

1. A single intravenous injection, the total duration of treatment therefore being approximately 10 seconds.
2. Four injections of Mapharsen within one day, at 2 hourly intervals.
3. Intravenous drip over a six hour period for one day only.
4. Two injections, at 4 1/2 hour intervals on each of two successive days.
5. Intravenous drip over a two-day period. On each of those days the drip was administered for two periods of 2 1/2 hours each, separated by a two hour rest period.
6. Single daily injections on four consecutive days.
7. Four injections at two hour intervals, on each of four consecutive days.
8. Six-hour intravenous drip administered on each of four consecutive days.
9. Injections every other day (3 times weekly) for a period of 4 weeks. This represents a total of 12 injections.

The Effect of the Method of Administration and the Duration of Treatment on the Toxicity, Therapeutic Efficacy and "Chemotherapeutic Index" of Mapharson in Rabbit Syphilis.

(The figures in this table are preliminary, based on incomplete data. However, it is not anticipated that the final values will differ significantly from those here indicated).

Method and Duration of Treatment	Results in Syphilitic Rabbits			4 Estimated "Chemotherapeutic Index" in Man. Maximal Tolerated Dose in Rabbits (mg./kg.) ÷ Therapeutic Dose in Current Use (mg./kg.)
	1 Maximal Tolerated Dose mg./kg.	2 Minimal Curative Dose mg./kg.	3 Margin of Safety: "Chemotherapeutic Index"	
<u>Intravenous drip</u>				
1 day (6 hrs.)	20	10 ⁶	2.0	
2 days	32	7 (?)	4.5	
4 days (6 hrs. daily)	48	12	4.0 ⁸	
5 days	-	-	5.0 ⁸	$\frac{55\checkmark}{20} = 2.75$
<u>Multiple doses daily</u>				
1 day ⁴	17	8 ⁶	2.0	
2 days ⁵	28	6	4.7	
4 days ⁴	40	3.6 (?)	11.0 (?)	
5 days	-	-	-	$\frac{45\checkmark}{15} = 3.0$
<u>Daily injections</u>				
1 day	10.0	7.0	1.4	
4 days	30	5.0	6.0	
12 days	70.0 ⁶	-	14.0 ⁸	$\frac{70\checkmark}{12} = 6.0$
<u>Injections every other day (3 times weekly)</u>				
4 weeks	96	8.0 ⁶	12	$\frac{96}{12} = 8.0$
6 weeks	144 ⁶	-	18 ⁸	$\frac{144\checkmark}{18} = 8.0$
<u>Weekly injections</u>				
6 weeks	60	8.0	7.5	
20 weeks	200 ⁶	-	26.0 ⁸	$\frac{200\checkmark}{20} = 10.0$

- 1 "Maximal Tolerated Dose" = amount which kills less than 5 per cent of animals.
- 2 "Minimal Curative Dose" = amount which cures more than 95 per cent of animals.
- 3 Two drip periods daily, each for 2 1/2 hours, separated by 2 hour rest period.
- 4 Four injections daily, at 2 hour intervals.
- 5 Two injections daily, at 4 1/2 hour intervals, and thus comparable with the 2 day intravenous drip schedule.
- 6 Estimated: data incomplete.
- 7 Estimated by extrapolation from experimental data.
- 8 In the absence of experimental data with respect to therapeutic efficacy, this figure is an estimate based on the assumption that, as indicated by the other experiments, the therapeutic dose will not differ significantly on the longer schedule.

Appendix E

To the Minutes of the 13th Meeting of the Subcommittee on Venereal Diseases
National Research Council

Dr. Ferrin H. Long, Chairman,
Committee on Chemotherapeutics and Other Agents
615 North Wolfe Street
Baltimore, Maryland.

January 14, 1942.

Dear Doctor Long:

On January 6 you returned to me for further consideration by the Subcommittee on Venereal Diseases the proposal of Doctors Arthur Schech and Lee Alexander for an evaluation of short term intensive arsenotherapy of early syphilis for ambulatory patients. Your committee had raised the issue that this was essentially a long term study requiring at least 5 years for completion, and that it seemed undesirable to embark upon any studies which did not have a possibility of being completed within a year and a half. Your committee also raised the issue as to the value of the proposal of Doctors Schech and Alexander from the point of view of studies of toxicity of the method of treatment proposed.

Acting on your request, I resubmitted the proposal of Doctors Schech and Alexander to the Subcommittee on Venereal Diseases at its meeting on January 13th.

The Subcommittee again voted to accept this application and to rate it "A".

As your committee justly points out, the results to be expected from this study may be divided into two parts: first, those dealing with the acute toxicity of the method; and second, those dealing with its therapeutic efficacy. The first of these, toxicity, is a problem which may be determined within the time period of a year and a half and which is, in the opinion of the Subcommittee on Venereal Diseases, of the utmost importance.

The work so far done on the intensive arsenotherapy of early syphilis strongly suggests that a method can be devised of materially shortening the time necessary for the treatment of the infection in this stage, and at the same time of materially reducing the high mortality rate which prohibits the routine adoption of existing intensive methods of treatment. The January 13th meeting of the Subcommittee on Venereal Diseases was devoted largely to a general discussion of this problem and eventuated in a motion, which was approved and which will be shortly transmitted to the Surgeon General of the Army through the proper channels, reading as follows:-

"MOVED THAT THE INTENSIVE ARSENOTHERAPY OF EARLY SYPHILIS (INCLUDING THE SO CALLED FIVE-DAY TREATMENT) 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 THE METHOD CANNOT AT PRESENT BE RECOMMENDED FOR ROUTINE USE BY THE ARMED FORCES."

There was presented to the Subcommittee on Venereal Diseases certain confidential information as to an experimental study in animals of intensive arsenotherapy which leads the Subcommittee to believe that the modification of treat-

ment proposed by Doctors Schoch and Alexander may be as satisfactory in clinical results as the somewhat shorter methods heretofore employed, and may at the same time eliminate the mortality rate which at present ranges somewhere between 1 in 200 and 1 in 400 patients treated.

The Subcommittee on Venereal Diseases believes therefore that it is of the utmost importance to the armed forces that an experience as to the acute toxicity of the proposed modification be gathered in the shortest possible period of time. The method to be used by Doctors Schoch and Alexander will parallel that in use in a number of other clinics, and its employment by them will permit an evaluation of toxicity in a much shorter period of time than would otherwise be possible.

As to the therapeutic efficiency and the feeling of the Committee on Chemotherapeutics and Other Agents that this is essentially a long term problem, the Subcommittee on Venereal Diseases agrees. My committee wishes, however, to point out that any worth while studies of syphilis, whether laboratory or clinical, are essentially long term studies; that this disease continues to be, as it always has been, one of the largest wasters of manpower in the armed forces; and that therefore long term studies looking toward elucidation of fundamental problems, particularly those concerned with treatment, are highly desirable of support. The Subcommittee on Venereal Diseases also felt that it would probably be possible for Doctors Schoch and Alexander to arrange for the long term follow up of their treated patients, if not by themselves (assuming that they leave their present positions for commissions with Army or Navy) by their successors; and that such arrangements could almost certainly be made without the necessity of additional appropriations from the Office of Scientific Research and Development.

The Subcommittee on Venereal Diseases feels further, however, that if the proposal of Doctors Schoch and Alexander is accepted, these workers should be requested to center their efforts on the two problems of toxicity and therapeutic efficiency without adding the complicated features of the possible protecting effect of thiamin hydrochloride and vitamin C on reactions. We therefore suggest that if the proposal of Doctors Schoch and Alexander is acceptable on an "A" basis to your committee and by the Committee on Medicine, the sum to be granted be reduced by the amount of \$600. (the amount specified for the purchase of thiamin hydrochloride and vitamin C), and that the grant be made to Doctors Schoch and Alexander in the amount of \$3050.

With this discussion and these modifications, the proposal of Doctors Schoch and Alexander is herewith returned to you, again accepted by the Subcommittee on Venereal Diseases, and again rated as "A". The favorable consideration of your committee and of the Committee on Medicine is respectfully requested.

Sincerely yours,

J. E. More, M.D., Chairman,
Subcommittee on Venereal Diseases.

Cc: Doctors Larkey,
Cushing
Pepper

Appendix "F"

To the Minutes of the 13th Meeting of the Subcommittee on Venereal Diseases
National Research Council

January 14, 1942.

Dr. Perrin H. Long, Chairman,
Committee on Chemotherapeutics and Other Agents,
615 North Wolfe Street
Baltimore, Maryland.

Dear Doctor Long:

At a meeting of the Subcommittee on Venereal Diseases on January 13, 1942, there was considered a proposal of Doctors Charles M. Carpenter and Stafford L. Warren, University of Rochester School of Medicine and Dentistry, for a study of the toxicity and therapeutic efficacy of mapharsen and neoarsphenamine at fever temperatures in experimental syphilis in rabbits.

This proposal was accepted by the Subcommittee on Venereal Diseases and was rated "A".

The reasons advanced by the Subcommittee for the acceptance of this proposal are as follows:-

There is already existing a body of clinical and experimental evidence to indicate that in both human beings and experimental animals the combination of fever therapy and chemotherapy is more effective than either one alone. For the most part, however, the evidence in the literature, both clinical and experimental, is incomplete and inconclusive. Carpenter and Warren themselves have, together with Boak, carried out a study now in press which indicates that experimental syphilis in rabbits can be cured by a mode of therapy combining a single subcurative dose of neoarsphenamine with a single subcurative session of artificial fever. The experiments so far completed by Carpenter, Warren, and their associates, are nevertheless still far short of the desirable in evaluating the optimum relationship between drug dosage and height and duration of fever; nor does evidence permitting any satisfactory conclusions on these points exist elsewhere in the literature.

It seems entirely possible to the Subcommittee on Venereal Diseases that utilizing the combination of chemotherapy and fever therapy, a method of treatment of early syphilis in experimental animals, and therefore perhaps also in human beings, may be elaborated which will permit cure of the disease in one day.

The present proposal of Doctors Carpenter and Warren should therefore be regarded as an integral part of a concentrated effort to solve the urgent problem of the intensive arsenotherapy of early syphilis; and as such, of major importance to the armed forces.

As you doubtless know, Doctors Carpenter and Warren submitted two applications, one of which, for the experimental study referred to here, the other a proposed clinical study. The Subcommittee on Venereal Diseases rejected the

application for the clinical study for the reasons given in a letter to Doctors Carpenter and Warren, a copy of which is enclosed herewith. The Subcommittee believes that clinical experimentation in this important field should properly await the completion of the fundamental laboratory studies described in the enclosed proposal.

The Subcommittee on Venereal Diseases believes further that Doctors Carpenter and Warren are the best qualified persons in the country to carry out such a study as this. Dr. Warren has had more experience with fever therapy in experimental animals than any other investigator; and Dr. Carpenter has an adequate familiarity with experimental syphilis in the rabbit.

The favorable consideration of your Committee and that of the Committee on Medicine is therefore urgently requested.

Very truly yours,

Cc: Dr. Pepper
Dr. Cushing
Dr. Larkey

J. E. Moore, M.D., Chairman,
Subcommittee on Venereal Diseases.

Appendix "G"

To the Minutes of the 13th Meeting of the Subcommittee on Venereal Diseases
National Research Council

ON THE LABORATORY DIAGNOSIS OF LYMPHOGRANULOMA VENEREUM

Only one diagnostic procedure for lymphogranuloma venereum, the intradermal test of Frei, has as yet come into general use. Other methods used in confirming the diagnosis are either impractical (animal inoculation, artificial cultivation of the virus), nonspecific (alterations in serum protein), or their value not yet established (complement fixation).

Frei tests:-These are skin tests, which may be performed with various "antigens", as follows:-

1. Pus obtained from an unruptured bubo from an acute case of lymphogranuloma venereum. This pus must be diluted 1 - 5 or 1 - 10, cultured for sterility, heated for 1-2 hours on consecutive days at 58° C., a preservative added, and the material placed in sterile rubber-stoppered vials. This material is then tested upon known positive cases and known negative controls to determine its potency. Pus from different patients differs in antigenic potency. When human bubo-pus antigens are locally available they may be used, but are not generally recommended for use by the armed forces because of uncertainty of sources of supply and variability of antigens.

2. Mouse brain antigen (Lederle Laboratories). This preparation is commercially available. It is not, however, recommended for use by the armed forces, because of the high proportion of nonspecific results obtained.

3. Chick embryo antigen. This is the preparation recommended for Frei testing.

Comparison of chick-embryo antigen with human bubo-pus and mouse-brain antigens:- Enough evidence has accumulated to suggest that chick embryo (yolk sac) antigen is equal in specificity and sensitivity to mouse-brain antigen; and that it is probably less sensitive, though equally specific, with the most potent human bubo-pus antigens. As with mouse-brain antigen, nonspecific papules (5-7 mm. in diameter) are relatively common with yolk-sac antigen (about 5 - 10 per cent).

Method of use of chick-embryo antigen:- This preparation is supplied in two ampules, one of which is the virus containing antigen, the other the non-virus-containing yolk sac control. For use in Frei testing 0.1 c.c. of antigen and 0.1 c.c. of control material are injected intradernally into different areas on the flexor surface of the forearm. The areas chosen should be at least 4 cm. apart, or the virus antigen and control may be injected in opposite forearms. Separate tuberculin syringes and 26 gauge needles should be used.

Reading of results:- The injected areas must be inspected 48 and 72 hours later. A positive reaction consists in a more or less indurated papule

7 mm. or more in diameter (disregarding the surrounding zone of erythema), with or without central vesiculation or ulceration. A doubtful reaction consists in a papule roughly from 5 to 7 mm. in diameter, without central ulceration or vesiculation. A negative reaction consists in no change at the injected site, or erythema only, or a papule less than 5 mm. in diameter. If the control material likewise yields a positive papule (7 mm. or over), the Frei test should be repeated with human bubo-pus antigen if it is available.

The test may be read as positive or doubtful if the papular reaction described occurs only with the virus-containing antigen, the control remaining negative.

Interpretation of results:- The Frei test is of greatest value in patients with the acute bubonic form of lymphogranuloma venereum where a negative test may be observed gradually to develop into a positive one.

There is reason to believe that in certain instances there are non-specific cross-reactions in other venereal diseases, e. g., chancroid, granuloma inguinale, syphilis (Robinson, South. M. J., 33: 144, 1940); Brandt and Torpin, Am. J. Syph. & Ven. Dis. 24: 632, 1940); and a positive Frei test with any antigen must be interpreted with caution when suspected lymphogranuloma venereum co-exists or may be confused with these diseases.

Still further, a positive Frei test cannot be relied upon absolutely to establish the lymphogranulomatous nature of any clinical condition, since it is known that in untreated infections with lymphogranuloma venereum, skin sensitivity persists for many years, probably for a life time. A positive test may therefore mean only that the patient has had lymphogranuloma venereum at some time in the past, rather than that his presenting symptoms are caused by this disease.

In short, the Frei test is of most diagnostic value when it is negative, since under these circumstances lymphogranuloma venereum, past or present, may be excluded with reasonable certainty.

Appendix H

To the Minutes of the Thirteenth Meeting of the Subcommittee on
Venereal Diseases, National Research Council

At the request of the Chairman, Subcommittee on Venereal Diseases, Doctors Hyman, Webster, and Thomas met in New York City in an effort to resolve the discrepancy between the figures presented at the meeting by Doctors Hyman and Webster. A new tabulation was made in which these three observers apparently concur. The patients were first subdivided into two groups: (a) those observed until the date of relapse or, if no relapse, until June 30, 1941; and (b) those lost from observation prior to June 30, 1941. The patients lost from observation were further subdivided on the basis of the length of time followed from the date of treatment until the date of the last observation.

From these data submitted to the Chairman by Doctors Thomas and Webster it was possible to evolve a table showing the results of the continuous intravenous drip treatment in the Mount Sinai patients, including all patients followed until relapse, or if no relapse, for at least one year after treatment.

These data are appended herewith.

(See reverse)

Mapharsen 1200 milligram series
(original treatment only)

Total patients treated	Number observed until date of relapse (clinical or serologic), or, if no relapse, for at least 1 year after treatment		Number lost from observation in less than 1 year	
109	69		40	
400 - 1100 milligram series				
148	107		41	
Status of patients followed until relapse, or if none, for at least one year 1200 milligram series				
	Of these			
Total	Clinical and serologic "cure"	Still seropositive no clinical relapse	Serologic relapse	Reinfection or infectious relapse
69	59 (85.5%)	0 —	1 (1.4%)	9 (13.0%)
400 - 1100 milligram series				
107	79 (73.8%)	8 (7.3%)	3 (2.8%)	17 (15.8%)

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WITHOUT THE PERMISSION OF
NATIONAL RESEARCH COUNCIL

C O R R E C T I O N

There is an important error in line 5 of page 7 of the Minutes of the Thirteenth Meeting of the Subcommittee on Venereal Diseases, National Research Council held January 13, 1942. The phrase in which the error occurs is as follows:

"....that at least 10 per cent, if not more, other patients have developed serious toxic reactions, usually toxic encephalopathies, followed by recovery;"

The figure of 10 per cent is incorrect. The correct figure is 1.0 per cent.

This letter should be appended to your copy of the Minutes of the 13th meeting.

J. E. Moore, M.D., Chairman,
Subcommittee on Venereal Diseases.

Cc: To all Members of the Subcommittee
on Venereal Diseases, National Research Council
and other Officials who received copies of the Minutes.

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Subcommittee on Venereal Diseases.

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on Venereal Diseases, National Research Council
and other Officials who received copies of the Minutes.

NATIONAL RESEARCH COUNCIL

DIVISION OF MEDICAL SCIENCES
COMMITTEE ON MEDICINE

SUBCOMMITTEE ON VENEREAL DISEASES

Minutes of Meeting
December 5, 1941.

The 12th meeting of the Subcommittee on Venereal Diseases, National Research Council, was held in Washington, December 5, 1941. Present were the following members of the Subcommittee: Dr. Moore (Chairman), Doctors Alyea, Cox, Mahoney, Nelson, and Stokes; also Doctors Weed, Long, Pepper, Cushing, and Larkey of the National Research Council; also Colonel Anderson, and Lieutenant Colonels Simmons, Callender, Kimbrough, Majors Seeley and Stone, and Captain Gordon, U. S. Army; also Lieutenant Colonel Eanes, Selective Service; also Doctors Dochez, Hastings, and Walker of the Committee on Medical Research; and Dr. McDowd of the American Red Cross.

The meeting opened with a discussion of proposals for grants in aid for research submitted to the Subcommittee on Venereal Diseases. Doctors Weed and Pepper described the mechanism for consideration of these proposals and the Subcommittee was instructed that proposals should be rejected or accepted and, if accepted, that they should be given priority ratings of A, B, or C. Following the initial explanation, 20 applications for funds were discussed and the following action taken:

- 1) The proposal of Dr. Abraham Cantor of the Department of Public Health and Preventive Medicine, University of Pennsylvania, for the purpose of studying the diagnosis of gonorrhea and non-gonorrheal genito-infectious lesions in the female, was considered and action on it postponed pending further information to be obtained by the Chairman. The Chairman has written to Dr. Cantor requesting him to supply all members of the Subcommittee with reprints of certain articles to which he refers in his application and to describe in more detail

his proposed plan of attack. When this information is available it will be circularized to members of the Subcommittee, and action on Dr. Cantor's application taken by mail.

2) The proposal of Dr. Robert Greenblatt of the University of Georgia School of Medicine for the sum of \$3,000. for each of two or three years, for the purpose of further investigations in the diagnosis, treatment, and prevention of newer venereal diseases (chancroid, granuloma inguinale, and lymphogranuloma venereum) was approved and given the rating of A (urgent).

3) The proposal of Dr. Murray Sanders, College of Physicians and Surgeons Columbia University, for \$6,800. for a period of one year, for the purpose of a study of the epidemiology of lymphogranuloma venereum with especial reference to the carrier problem, was approved and given the rating of A (urgent).

4) The proposal of Dr. Bruce Webster, New York Hospital and Cornell University Medical School, for a social service and psychiatric study of delinquent clinic patients with syphilis, was rejected.

5) The proposal of Dr. J. Howard Mueller of the Harvard Medical School for the sum of \$5,800. for one year, for the purpose of studying the growth requirements of the gonococcus, was accepted and given the rating A (urgent).

6) The proposal of Dr. John D. Williams, Massachusetts Institute of Technology, for a study of the growth of Spirocheta pallida in vitro was rejected.

7) The proposal of Dr. Wolfgang A. Casper, unattached, for a study of the biological and chemical characteristics of the gonococcus with particular emphasis on type specific carbohydrate fraction as a means of rendering protection in the human organism against gonorrhoea, was rejected.

8) The proposal of Dr. Fred L. Adair and Lucile R. Hac, University of Chicago, for a study of gonococcal infection as to diagnosis, treatment, and the biology of the gonococcus, was rejected.

9) The proposal of Doctors Charles M. Carpenter and Herbert E. Stokinger, University of Rochester School of Medicine and Dentistry, for the development of synthetic media for cultivation of the gonococcus, was rejected.

10) The proposal of Doctors Charles M. Carpenter and Herbert E. Stokinger, University of Rochester School of Medicine & Dentistry, for a biochemical investigation of sulfonamide-fastness of the gonococcus, was rejected.

11) The proposal of Doctors Charles M. Carpenter, Stafford L. Warren, M. E. Winchester, and R. A. Vonderlehr, University of Rochester School of Medicine & Dentistry, for the sum of \$14,500. for a period of one year, for the purpose of a study of the control of gonococcal infection in the U. S. Public Health Service demonstration area in Glyn County, Georgia, was accepted, and was given the rating C (not urgent).

12) The proposal of Doctors Charles M. Carpenter, Stafford L. Warren, M. E. Winchester, and R. A. Vonderlehr, University of Rochester School of Medicine & Dentistry, for the sum of \$9,000. for a period of four months for a study of the treatment of early syphilis with organic arsenic compounds and fever therapy, was discussed. It was voted that in the opinion of the Subcommittee this application with modifications represented an important piece of work which, in all probability, should be accepted with rating A (urgent).

It was further voted to return this application to the applicants with the request for further information on two points:

a) It was felt that the study should be limited to patients with early rather than with latent syphilis, and since some doubt was expressed as to whether a large enough series of patients could be amassed in Glyn County, Georgia, within the period specified, the applicants were asked either to provide estimates that such material is available, or to alter the time period of the study.

b) The applicants were asked further to guarantee assurance from the Glyn County Health Department and from the U. S. Public Health Service that a five-year follow up of treated patients by competent syphilologists would be provided.

c) The Subcommittee felt that laboratory data regarding the toxicity and therapeutic efficiency of arsenical drugs at varying temperature levels are so far inadequate; that the laboratories of the applicants are equipped to carry out such a study; and the applicants were therefore asked to include a proposal for a laboratory investigation to run concurrently with the clinical investigation.

If these suggestions are accepted by the applicants and the application resubmitted, it will be circularized among the members of the Subcommittee by mail with a tentative understanding that it will be accepted and rated as A (urgent).

13) The application of Dr. Frank C. Combes, New York University (Bellevue Hospital), for the sum of \$2600. for a period of one year, for a study of the value of intravenous injections of Frei antigen and of formol-gel test in diagnosis of lymphogranuloma venereum, was considered. The Subcommittee felt that further information was desirable, and the Chairman was authorized to request of Dr. Combes a survey of the literature covering these two procedures, and a summary of his own experience with the methods. When this information is available it will be circularized by mail among the members of the Subcommittee, and the application further considered.

14) The application of Dr. Herbert Lund of the Institute of Pathology, Western Reserve University, for the sum of \$3090.50 for a study of the quantitative determination of small quantities of reagin not detectable by ordinary serologic procedures, and of the significance of such determinations in the diagnosis of syphilis, especially in those cases classed as seronegative, was approved and rated as A (urgent).

15) Lieutenant Armand S. Pereyra, M.C., U. S. Navy, did not submit a formal application for a grant in aid to the Subcommittee on Venereal Diseases, but did write letters descriptive of his work on the prophylaxis of venereal disease by electrophoresis. The possible implications of this work seemed to the members of the Subcommittee so important that prior to the meeting on December 5, Captain Charles S. Stephenson, Director of the Division of Public Health, Bureau of Medicine and Surgery, U. S. Navy, had been informally requested by the Chairman of the Subcommittee to arrange for Lieut. Pereyra's relief from his present assignment, and his assignment on a duty status to the laboratory of Dr. John F. Mahoney, Senior Surgeon, U. S. Public Health Service, Stapleton, Staten Island, for the purpose of prosecution of laboratory investigations in this field. The permission of the Surgeon General, U. S. Public Health Service and of Dr. Mahoney having been obtained to this assignment, it is understood that Captain Stephenson has already requested the necessary orders from the Surgeon General, U.S.Navy. The Subcommittee voted to thank Captain Stephenson for his prompt action in this case.

16) The proposal of Doctors Chester J. Farmer, Arthur F. Abt, and Hans Aron, Northwestern University Medical School, for a study of the possible synthesis of ascorbic acid compounds of arsphenamine and their therapeutic effect in syphilis, was rejected.

17) The proposal of Doctors R. H. Broh-Kahn and I. Mirsky of the May Institute for Medical Research, the Jewish Hospital, Cincinnati, for a study of the growth requirements of the gonococcus and meningococcus, was rejected.

18) The proposal of Dr. Frank Cosmia, Stanford University School of Medicine, San Francisco, for a study of the problem of hemorrhagic encephalitis from the arsphenamines, especially from massive dose therapy, was rejected.

19) The proposal of Doctors Arthur Schoch and Lee Alexander of Baylor University Medical School of the Dallas Syphilis and Venereal Disease Clinic, Dallas,

Texas, for qualitative and quantitative studies of syphilitic reagin, was rejected.

20) The proposal of Doctors Arthur G. Schoch and Leo Alexander of Baylor University Medical School and the Dallas Syphilis and Venereal Disease Clinic, Dallas, Texas, in the approximate amount of \$3650. for a period of one year, for a study of the evaluation of short term intensive arsenotherapy of early syphilis for ambulatory patients, was provisionally accepted and rated as A (urgent), subject to the provision that Doctors Schoch and Alexander modify their proposed treatment scheme in the direction of laboratory evidence which the Chairman of the Subcommittee provided confidentially to the members. The Chairman was authorized to write to Doctors Schoch and Alexander to this effect.

(21) Dr. Moore, Chairman of the Subcommittee, submitted for general discussion a research project contemplated in the Syphilis Division of the Johns Hopkins Hospital and University for the study of nonsyphilitic genital lesions (chanroid, granuloma inguinale, and lymphogranuloma venereum). Dr. Moore did not submit to the Subcommittee an application for funds in aid of this project, since funds are already available for the purpose. It was pointed out, however, that because of the depletion of the staff of the Syphilis Division by the loss of five of its members to the Army and Navy, additional professional personnel would be required to carry the study to completion. For this reason Dr. Moore requested of the Subcommittee approval of a request from him, through the Committee on Medicine, to the Surgeon General, U. S. Army, for the release from his present duties and temporary assignment to the Syphilis Division, Johns Hopkins University and Hospital, of First Lieutenant Lawrence Katzenstein, M.C., U.S.A., now stationed at the Station Hospital, Fort George G. Meade, Maryland. Lieutenant Katzenstein is a former member of the staff of the Syphilis Division, and thoroughly equipped for participation in research project.

It was pointed out by Major Seeloy that the granting of such a request would be contrary to Army practice. Nevertheless, it was further pointed out by the Chairman that assignments similar to this had been made by the U. S. Army Medical Corps during World War No. 1 in 1917-19, and that the U. S. Navy Medical Corps was on the point of making a similar assignment in the case of Dr. Armand J. Pereyra, U.S.N. referred to above. With this explanation the approval of the Subcommittee for Dr. Moore's request was granted. A letter from Dr. Moore to the Surgeon General U. S. Army has been written, as follows:-

Surgeon General
U. S. Army
War Department
Washington, D.C.

December 12, 1941.

Through Dr. O. H. Perry Pepper, Chairman,
Committee on Medicine, National Research Council.

Sir:

At a meeting of the Subcommittee on Venereal Diseases, National Research Council, on Friday, December 5, I presented for discussion a proposal for a study of nonsyphilitic genital lesions (chancroid, lymphogranuloma venereum, and granuloma inguinale). A protocol of this study is enclosed herewith. The project has been discussed with Lieutenant Colonel Harry Plotz, Chief of the Virus Laboratory, Army Medical School. Both Lieutenant Colonel Plotz and the Subcommittee on Venereal Diseases feel that the proposed study is one of importance to the U. S. Army and Navy.

Funds for the prosecution of this study are not necessary through the National Research Council or other sources, since such funds are already available in the budget of my Department. However, the prosecution of the research project is at present materially impeded by a shortage of professional personnel, caused by acceptance of commissions in the U.S. Army or Navy by five physicians on my staff. One of these physicians, First Lieutenant Lawrence Katzenstein, M.C., U.S.A., is now on active duty at the Station Hospital, Fort George G. Meade, Maryland.

The Subcommittee on Venereal Diseases has formally approved a request from me, as Physician in charge of the Syphilis Division, Johns Hopkins University and Hospital, to the Surgeon General U. S. Army, that First Lieutenant Lawrence Katzenstein be relieved from his present duties at Fort George G. Meade and temporarily assigned to the Syphilis Division, Johns Hopkins University and Hospital, for the purpose of prosecution of this research project. I have the honor, therefore, to submit such a request.

Respectfully submitted,

J. E. Moore, M.D., Chairman,
Subcommittee on Venereal Diseases.

The Subcommittee then considered the order of priority which it wished to indicate for those applications accepted and rated as A. This order of priority was expressed as follows: (1) Greenblatt, (2) Mueller, (3) Schoch and Alexander, (4) Lund, and (5) Sanders.

There was then considered a telegraphic request from Dr. Harold Thomas Hyman, New York, to the Chairman of the Subcommittee for the right of a personal appearance by Dr. Hyman before the Subcommittee to discuss the intensive arsenotherapy of early syphilis. After considerable discussion the Chairman was authorized to write to Dr. Hyman thanking him for his offer and requesting him, in view of the uncertainty of the date of the next meeting of the Subcommittee, to submit in writing to all members of the Subcommittee any additional unpublished information on the topic, together with an expression of his personal point of view.

Major Seeley announced that arrangements had been made to supply all Medical Officers in the active service of the U. S. Army with copies of the Army Medical Bulletin.

There followed a discussion of the question of performance of serologic tests for syphilis in U. S. Army and Navy laboratories. As a result of this discussion the following recommendation was approved:

IT IS RECOMMENDED THAT THE ARMY AND NAVY INSTITUTE AS PROMPTLY AS POSSIBLE SURVEYS OF SERODIAGNOSTIC PERFORMANCE IN THE LARGER SEROLOGIC LABORATORIES OF THE TWO SERVICES, UTILIZING AS CONTROL LABORATORIES THE LABORATORIES OF THE ARMY MEDICAL SCHOOL AND THE NAVY MEDICAL CENTER, PLUS ALSO THE LABORATORIES OF THE SEROLOGIST ORIGINATORS OF THE SEVERAL TECHNIQUES EMPLOYED. THE SYSTEM OF SURVEYS SHOULD CONFORM WITH SUCH MODIFICATIONS AS MAY BE NECESSITATED BY SPECIAL ADMINISTRATIVE DETAIL TO THE RECOMMENDATIONS OF THE COMMITTEE FOR EVALUATION OF SERODIAGNOSTIC TESTS FOR SYPHILIS. WHEN THIS PRELIMINARY SURVEY OF LARGER LABORATORIES HAS BEEN COMPLETED, DESIGNATED LABORATORIES IN CORPS AREAS OR NAVAL DISTRICTS SHOULD BE SELECTED TO EXTEND THE SYSTEM OF SURVEYS OF SERODIAGNOSTIC PERFORMANCE TO SMALLER LABORATORY UNITS.

There was next considered a memorandum on the laboratory diagnosis of lymphogranuloma venereum intended for circularization to all Medical Officers of the U. S. Army and Navy. The Chairman was directed to submit this memorandum to Dr.

Borris Kornblith, New York, and to Dr. Robert S. Greenblatt, University of Georgia School of Medicine, for their comments; and to recircularize members of the Subcommittee with the revised version.

There followed a further consideration of the problem of induction of syphilitic selectees into the U. S. Army. The recommendation of the Subcommittee on Venereal Diseases made at its Eleventh Meeting has already been incorporated into the revised copy of M 1-9 about to be issued by the U. S. Army. The point of view of Selective Service was presented by Lieutenant Colonel Eanes, who pressed for a relaxation of certain of the requirements included in the present recommendation, particularly with respect to the requirement of a spinal fluid examination, and to the requirement of the total amount of treatment obligatory before induction. Since the point of view of Selective Service, as expressed by Colonel Eanes, and the point of view of the Army Medical Corps, as expressed by Colonel Anderson, were still divergent, a motion was passed by the Subcommittee on Venereal Diseases to the following effect:

IT WAS MOVED, SECONDED, AND PASSED THAT A DECISION AS TO HOW MANY SYPHILITIC PATIENTS AND WHAT TYPE OF SYPHILITIC INFECTION WILL BE ACCEPTED UNDER THE SELECTIVE SERVICE ACT BY THE U. S. ARMY, MUST BE A MATTER FOR ADMINISTRATIVE AGREEMENT BETWEEN THE SURGEON GENERAL AND CHIEF OF STAFF, U. S. ARMY, AND THE DIRECTOR OF SELECTIVE SERVICE.

The meeting adjourned at 5:15 P.M.

12-541

MINUTES OF THE ELEVENTH MEETING OF
THE SUBCOMMITTEE ON VENEREAL DISEASES

of the .

NATIONAL RESEARCH COUNCIL

The eleventh meeting of the Subcommittee on Venereal Diseases of the National Research Council was held in Washington, September 12th, 1941. Present were the following members of the Subcommittee: Doctors Stokes (Acting Chairman), Alyea, Clarke, Cox, and Nelson; also Doctors Larkey, Long and Pepper of the National Research Council; Lieutenant Colonels Eanes (Selective Service), Kimbrough and Simmons, Major Seeley, Captains Gordon and Wayne, U.S. Army; Captain Stephenson, and Lieutenant Mast, U.S. Navy; Doctors Vonderlehr and Anderson of the United States Public Health Service.

As copies of the minutes of the last meeting had been sent to the members they were approved without being read at the meeting.

The first subject presented for discussion was the question of accepting into the Army selectees with latent syphilis.

Voted to substitute the term "Mapharsen" in place of "arsenoxide", wherever the latter has been used in the recommendations of this Subcommittee.

The Subcommittee expressed itself as being of the opinion that the so-called "long form" which had been prepared by Doctor Stokes, and of which copies had been sent to the members of the Subcommittee, was to serve as a standard treatment for guidance of officers in the service, but was not to apply to selectees. As the form contained only recommendations that had previously been approved by the Subcommittee, the form as prepared by Doctor Stokes was approved without discussion.

Continued on Next Fiche!

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MINUTES OF THE ELEVENTH MEETING OF
THE SUBCOMMITTEE ON VENEREAL DISEASES

of the .

NATIONAL RESEARCH COUNCIL

The eleventh meeting of the Subcommittee on Venereal Diseases of the National Research Council was held in Washington, September 12th, 1941. Present were the following members of the Subcommittee: Doctors Stokes (Acting Chairman), Alyea, Clarke, Cox, and Nelson; also Doctors Larkey, Long and Pepper of the National Research Council; Lieutenant Colonels Eanes (Selective Service), Kimbrough and Simmons, Major Seelzy, Captains Gordon and Whayne, U.S. Army; Captain Stephenson, and Lieutenant Mast, U.S. Navy; Doctors Vonderlehr and Anderson of the United States Public Health Service.

As copies of the minutes of the last meeting had been sent to the members they were approved without being read at the meeting.

The first subject presented for discussion was the question of accepting into the Army selectees with latent syphilis.

Voted to substitute the term "Mapharsen" in place of "arsenoxide", wherever the latter has been used in the recommendations of this Subcommittee.

The Subcommittee expressed itself as being of the opinion that the so-called "long form" which had been prepared by Doctor Stokes, and of which copies had been sent to the members of the Subcommittee, was to serve as a standard treatment for guidance of officers in the service, but was not to apply to selectees. As the form contained only recommendations that had previously been approved by the Subcommittee, the form as prepared by Doctor Stokes was approved without discussion.

The so-called "short form" which had been prepared by Doctor Stokes and Captain Gordon, the purpose of which is to be a guide to examining physicians, and to apply only to selectees, was then submitted for discussion.

The practicability of requiring a negative spinal fluid test for selectees with latent syphilis was discussed pro and con. Doctor Stokes pointed out that an unspecified percentage of men with latent syphilis develop syphilis of the central nervous system even though they have received the minimum amount of treatment as specified in the recommendations. Therefore, there was no way of excluding syphilis of the central nervous system previous to clinical manifestations without a spinal fluid examination. As it is desirable to keep such infections to the irreducible minimum it was voted to retain the negative spinal fluid test in the scheme of standards.

It was voted to revise Paragraph B to read: "Provided that, in infections estimated to be of less than 4 years' duration, registrants must have had a minimum total of 75 injections, at least 30 of which must have been an arsenical preparation and at least 40 an insoluble bismuth or its equivalent."

Voted to amend Paragraph C to read: "Provided that, in infections estimated to be of over 4 years' duration, registrants must have had a minimum total of 60 injections, of which at least 20 must have been an arsenical preparation and at least 40 an insoluble bismuth or its equivalent; rest periods between courses not to exceed 8 weeks."

It was voted to consider infections of unknown duration in registrants under 26 years of age to be of less than 4 years' duration and in registrants of over 26 years of age to be of more than 4 years' duration.

With Doctor Clarke dissenting, it was voted to retain the 20-20 standard (for the quiescent cases).

The question of requiring an affidavit from the treatment agency was then discussed. It was voted that a signed statement from a competent treatment source will be acceptable. The certificate must show the total number of doses of each drug, and the approximate calendar dates of administration, together with available clinical and laboratory data. A verbal report from a treatment source will not be acceptable as evidence of adequate treatment.

The short form, which reads as follows, was adopted:

Suggested Scheme of Standards
for Admission of Registrants with Syphilis

Registrants with (1) confirmed positive serologic tests for syphilis and no clinical manifestations of the disease; or (2) with convincing histories of a trustworthy diagnosis of syphilis; or (3) of treatment for the disease on serologic or clinical grounds or even though such evidence may possibly have been inadequate, may be considered for Class I-A --

- (a) Provided that a negative spinal fluid since infection and treatment has been reported from a trustworthy source; and
- (b) Provided that in infections estimated to be of less than 4 years' duration, at least 30 to 40 arsenical and 40 to 60 insoluble bismuth injections or its equivalent, with a minimum total of 60 injections have been given in alternating courses; rest periods between consecutive courses not exceeding 3 weeks, being allowable.

Evidence of duration of the infection shall be weighed by the examiner with due regard for age, general venereal history and medical guidance of the registrant.

In infections of unknown duration it shall be presumed for classification purposes that those of registrants under 26 years of age are of less than 4 years' duration, and over 26 years, of more than 4 years' duration.

In congenital infections and in acquired infections of more than 10 years' duration, in which no clinical progression occurred since treatment was begun; and in which a normal spinal fluid and negative physical examination is recorded not less than 2 years after treatment was terminated, the infection shall be regarded as "quiescent", and the registrant eligible for Class I-A; provided the treatment in question shall have included 20 arsenical and 20 heavy metal injections.

For the determination of treatment, the signed statements of acceptable treatment sources administering it with total number of doses of each drug and approximate calendar dates of administration and available laboratory and clinical data shall be required as evidence.

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The first business on the agenda after luncheon was a thumbnail sketch by Captain Stephenson of his recent trip to Great Britain. His vivid description of the nine-and-a-half-hour flight from Newfoundland to Scotland was most entertaining. He stated that, whereas the venereal disease rate during World War I was 26 per 1000, it is at the present time but 9.2 per 1000. However, the venereal disease rate in the Near East is extremely high. This matter is causing the Navy considerable concern. It is extremely difficult for soldiers

to get leave to London, where there are apparently but few professional prostitutes. Although most of the railroad stations are badly damaged, the road beds are in good condition and travel is surprisingly easy. Food and clothing are rigidly rationed. Eggs are particularly rare, and there is no Scotch whiskey available. The sanitation in the subway shelters is very good. Captain Stephenson made a special point to observe the morale of the people. This he found to be excellent everywhere. Parenthetically, he reported that neoarsphenamine is now being administered to patients at sea. Heretofore this had not been done. He reports a high rate of toxicity, due in his opinion to too rapid and too frequent treatment.

Doctors Pepper and Long then explained to the Subcommittee the method of making application for research projects pertaining to national defense. After considerable discussion the following members of the Subcommittee were appointed committees of one to submit to the Subcommittee research projects: Doctor Stokes, syphilis; Doctor Cox, gonorrhoea; Doctor Clarke, the other venereal diseases.

The next business was a consideration of the reports of the surveys in Kansas, Missouri, Nebraska, South Carolina, Georgia, West Virginia, Washington and Oregon. Each change proposed by the Editorial Committee, Doctor Vonderlehr, and the authors was discussed in considerable detail. All changes in the reports voted by the Committee were indicated on the original copies by the Acting Chairman. All eight reports were approved as amended, whereupon they were turned over to Doctor Larkey.

Upon the advice of the representatives of the Army it was voted to consider at the next meeting the question of the alleged demotion of noncommissioned officers who acquire a genital infection. It was

the consensus that the Committee should make a specific recommendation to the Secretary of War, after discussing the matter unofficially with the Surgeon General, that this practice be discontinued, as it is not in keeping with the present policy of doing away with punitive measures, and will result in much gonito-infection being inadequately treated.

THE MINUTES OF THE TENTH MEETING OF THE SUBCOMMITTEE
ON VENEREAL DISEASES OF THE NATIONAL RESEARCH COUNCIL

The stated meeting of the Venereal Disease Subcommittee of the Medical Sciences Division of the National Research Council was called by Dr. Lewis Weed for July 25th, ^{1941,} and was called to order by the temporary chairman, Dr. John H. Stokes, on that date at 10 a.m. at the offices of the National Research Council, 2101 Constitution Avenue, Washington, D.C. In addition to the Acting Chairman, the following were present: Doctors Alyea, Clarke, Cox, Mahoney, and Nelson, of the Venereal Disease Subcommittee of the National Research Council; also Doctors Larkey, Pepper, Richards, and Weed, of the National Research Council; Colonels Anderson, Cook, Hillman, Kimbrough, and Simmons, and Captain Gordon, United States Army; Lieutenant Mast, United States Navy; and Doctor Usher of the United States Public Health Service.

The first order of business, as indicated by correspondence of Dr. Joseph Earle Moore, Chairman, under date of June 28th, and Dr. John H. Stokes to Dr. Lewis H. Weed, dated July 10th, concerned Colonel Hillman's request in behalf of the Surgeon General's Office of the Army for an expression from the Committee on the subject of admission of men with acute gonorrhoea and of selectees with presumably latent syphilis without physical signs but with positive blood tests. It was particularly desired by the Surgeon General's Office to have from the Committee a statement of what might be regarded as adequate pre-induction standard treatment for syphilis which, if conformed to, would reasonably assure the continued latency of the disease, if possible without further treatment during the period of service.

Colonel Hillman, for the benefit of the Committee, restated the position of the Surgeon General's Office of the Army with respect to the questions raised. He pointed out that as long as the Selective Service System was expected to provide the Army with top-notch personnel from every standpoint, the A-1 classification should not include persons with potential disabilities such as latent syphilis, which might interfere both with their life expectancy and their subsequent usefulness in the Army of the future, including the reserves. He pointed out that if any standard of treatment could be explicitly defined which would assure that the Selectee who had conformed to it would be to all intents and purposes a normal individual requiring no further cognizance of his disease, he would be acceptable to the Army under the above ideal. Of course, if the situation became such that men with lower ratings than A-1 would have to be accepted, the situation with respect to syphilis could be reconsidered. Colonel Hillman indicated that the number of men involved at the present time in the syphilis selection question approximated 48,500. To indicate the progress made by the Surgeon General's Office in approaching a decision on the question, Colonel Hillman supplied the Chairman with a copy of a letter to the Adjutant General of the War Department from Lewis B. Hershey, Deputy Director of the Selective Service System, dated May 9, 1941, a copy of the text of which is herewith read into the minutes:

- "1. Under the provisions of MR 1-9, men suffering from acute gonorrhoea or having a positive serology may not be inducted into the Army. Knowledge of this fact is spreading and information has been received indicating that in certain parts of the country there is a growing practice of deliberately contracting gonorrhoea to avoid military service. Unless checked, this practice will prevent an equitable distribution of liability for service, and have a pernicious effect upon public health.

"2. Medical opinions have been submitted to this Headquarters indicating that --

"a. Under easily administered non-toxic treatment, acute gonorrhoea can be removed from the infectious stage in about 36 hours, and completely cured in one or two weeks in the large majority of cases.

"b. Regardless of a positive serology, practically all adequately treated syphilis will not break down and become active, is not infectious, and has no deteriorating effect upon the vigor and life expectancy of the individual.

"3. Under present regulations, Selective Service is unable to exert any corrective influence upon the situation, because if men suffering from a venereal disease were put in the deferred classification until cured and then reclassified as 1-A there is nothing to prevent them from again contracting infection and being rejected from service. Because of this, no reduction in voluntary infection can be expected until the reason for it is removed. On the other hand, as the knowledge spreads that gonorrhoea is an infallible cause of physical rejection and is easily cured, the number of cases will greatly increase. From every standpoint the evil of such a situation is apparent.

"4. Therefore it is recommended that MR 1-9 be amended so as to permit induction of --

"a. Men having acute recently acquired gonorrhoea.

"b. Men having positive serology when they can present a certificate from a reputable venereologist, clinic or State health department to the effect that they have received adequate treatment for syphilis as defined by the Surgeon General of the Army."

/S/ Lewis B. Hershey
Deputy Director

Colonel Hillman explained that this letter clarified the situation with respect to acute gonorrhoea which, when the recommendation for the amendment of MR 1-9 is adopted, would provide for the admission of selectees with acute gonorrhoea to the Army. He pointed out, however, that the situation with respect to syphilis was still undefined, inasmuch as the records of the Surgeon General's Office failed to indicate that the Subcommittee on Venereal Diseases had defined

with sufficient definiteness adequate standards of treatment by which the nonsignificance of the syphilis status of an individual with a positive serologic test could be judged. It was, therefore, he explained, the desire of the Surgeon General's Office to receive from the Committee a statement of standards which could be used as measuring sticks if and when it was decided to endorse the amendment of MR 1-9 with respect to the admission of selectees with syphilis.

Colonel Hillman further pointed out that the Surgeon General's Office felt that no standard of adequate treatment used in determining the admissibility of selectees should be lower than the standards of treatment adopted by the Surgeon General's Office for the Army as a whole, with respect to the adequate treatment of the disease in the Army personnel itself. Colonel Hillman felt the Army would be subject to criticism if adequacy on entering was not identical with adequacy after entering.

As stated above, Colonel Hillman indicated that men with acute gonorrhea will be inducted into the Army as soon as treatment facilities adequate to the problem are developed. It is evidently a considerable problem among Negro selectees. Certain additional hospital facilities will have to be provided for temporary retention purposes.

Colonel Hillman further pointed out that Army Medical Bulletin #43, in a presentation by Cooley (1938) described standards of treatment for syphilis which presumably expressed through the sponsorship of Moore, the standards of the Cooperative Clinical Group. It was felt that these standards are too high to govern the admission of men under the Selective Service Act, inasmuch as the minimum of treatment required was two years; the question was specifically raised as to whether the so-called 20-20 standard could be regarded as adequate in determining the admissibility of persons with latent syphilis.

The Chairman called for opinions of members. Dr. Mahoney was unwilling to commit himself. Dr. Nels Nelson pointed out that one third less than 48,000 of the selectees with syphilis would be kept out by other defects. Dr. Cox recalled that he had read a statement to the effect that 4% to 7% only of those having received the 20-20 standard of treatment would subsequently have trouble from the disease.

Colonel Hillman pointed out that a mere reduction in the number of selectees with syphilis was not what the Army desired, because on the present basis of selection it did not desire any persons with syphilis at all.

Dr. Clarke pointed out that standards of treatment for early, early latent and late latent syphilis had already been recommended to the Surgeon General's Office by the Subcommittee on Venereal Diseases, and suggested that the same systems be used in judging selectees.

Dr. Alyes pointed out that ultimately, if not now, the Army would be obliged to treat for syphilis some valuable men whom it might desire to induct.

Dr. Mahoney pointed out that age of the selectee changes the type of syphilis to be dealt with.

Colonel Hillman stated that in all probability at the present time, the 1-A classification will not be overdrawn.

Dr. Stokes stated that it had been in part his responsibility to provide for the Subcommittee the statement of treatment standards for early, early latent, and late latent syphilis, and that this had been done not in a verbally descriptive fashion, but as a record form which the Surgeon General's Office had subsequently apparently considered it inadvisable to adopt.

Colonel Hillman explained that this record form had not been adopted because it could not be made to fit into the syphilis register already in use in the Army.

Thereupon, upon request, Dr. Stokes undertook a verbal delineation of treatment standards for early, early latent, and late latent syphilis, impromptu. He began by pointing out that the so-called 20-20 standard (20 arsenical injections and 20 heavy metal injections) was in reality no standard at all, but an arbitrary statistical means employed for convenience in distinguishing, in tabulation and evaluation, between adequate and inadequate treatment. It was clear from subsequent work that in the 20-20 standard, the arsenical phase was over-emphasized and heavy metal inadequately represented. He suggested, therefore, that no attempts be made to interpret the fitness of selectees with latent syphilis in terms of a 20-20 standard, but that in its place a basis of 30-60 of continuous treatment (in the arsenical phase) be employed for seronegative primary and fully developed secondary syphilis, and also for early latency, meaning thereby the first four years of infection, if duration is known. He suggested that 40-80 be used as a standard for patients who have seropositive primary syphilis, or who had shown some clinical or serologic evidence of resistance in the treatment for an early infection. Finally he proposed that late latency, meaning thereby seropositive syphilis without clinical manifestations and with a negative spinal fluid, be treated by the standard suggested under Moore's sponsorship by the Cooperative Clinical Group; namely 24 arsenical injections in three courses of eight injections each, given without rest periods in alternation with heavy metal (bismuth) in ten-injection courses. The heavy metal treatment of latent cases should reach a minimum of sixty weeks of bismuth therapy, intermit-

tent after the close of the arsenical phase, and that where possible such treatment should be prolonged to eighty weeks and even longer in deference to the experience of the Western Reserve Clinic at Cleveland.

Dr. Stokes was instructed by the Committee to redraft these recommendations in writing for transmission to the Surgeon General's Office as the Committee's previously rendered opinion on adequate treatment for the phases of syphilis concerned in the United States Army.

Colonel Kimbrough then pointed out that it should not be forgotten that men under treatment for a venereal disease, and particularly for syphilis, are a debit and not an asset in an armed force, since they are to no small degree incapacitated by the demands of, and the effects of the treatment that they are actually receiving.

Colonel Hillman, in answer to a question, indicated that no specific mechanism such as a referee board or other device exists for reviewing the status of men with respect to their pre-admission adherence to standards of treatment for syphilis. It is to be presumed, therefore, that the passing on such a standard would be a function of the examining medical officer at the time of induction, and that it would have to be conducted in accordance with the standards to be supplied by the Surgeon General's Office, in accordance with the recommendations of the Venereal Disease Subcommittee.

Note: The question of a negative spinal fluid examination as part of the definition of latency, and ways and means for conducting such an examination under the conditions of medical examination for induction was, through oversight of the acting chairman, not brought up as part of the discussion. The importance of not accepting latent syphilitics, particularly early latent cases on the basis

of standards of previously received treatment without spinal fluid examination, is inescapable, and might lead to the induction of a number of preperetics, to mention no other category of the disease. The question of ways and means for securing spinal fluid examination before or after induction should therefore be carefully considered.

Colonel Hillman having assured the Subcommittee that the question of the induction of selectees with acute gonorrhoea could now be regarded as accepted in the affirmative, the discussion turned to the question of using certification by "a reputable venereologist" as part of the qualifying mechanism for the admission of latent syphilitics. (See Section 4-B of the above quoted letter of May 9th from the Selective Service System, signed Lewis B. Hershey, to the Adjutant General of the War Department.) It was agreed after discussion that owing to the impossibility of deciding what constituted a reputable venereologist, all reference to such should be excluded from the decision mechanism, as also any form of certification by clinics or state health departments. In its place it was recommended that a transcript or summary of the patient's treatment record, obtained from his physician, would constitute the basis of decision by the Surgeon General's Office or its authorized representative, including the examining medical officer. The recommendation as thus discussed was put in the form of a motion by Dr. Clarke, seconded and passed by the Subcommittee.

The next business before the Committee consisted of the reports drawn in behalf of the Committee on tours of inspection of the venereal disease control facilities of the following states:

Maryland (Cox and Stokes)	Washington (Stokes)
Kansas (Cox and Moore)	Oregon (Stokes)
Nebraska (Cox and Moore)	West Virginia (Nelson)
Missouri (Cox and Moore)	Georgia (Nelson)
	South Carolina (Nelson)

Mimeographed copies of these reports were in the hands of the Subcommittee members present at the meeting. Two reports, those on Washington and Oregon, were specifically marked confidential.

There being no stenographer present to record precisely the contributions of individual members of the Subcommittee through the discussion, the following is the Chairman's summation of the gist of the matter. The principal contributors to the discussion were Doctors Nelson, Clarke, Stokes (Acting Chairman), Cox, Alyea, and Usher, representing Dr. Vonderlehr, United States Public Health Service Division of Venereal Diseases. There were present during parts or the whole of this discussion, Dr. Pepper, Chairman of the Medical Committee, and Dr. Weed, Chairman of the Medical Sciences Division of the National Research Council, both of whom also participated in the discussion.

The Acting Chairman inquired whether the Subcommittee desired to express itself first on the reports as a whole, or to take them up individually as an introduction to the subject. The discussion took a general trend -- Doctors Nelson, Clarke, Stokes and Alyea pointing out that in their present form, the reports made sweeping recommendations and exceedingly forceful condemnations of facilities, procedure and so forth, which in some cases at least appeared to be based upon what might legally and technically be called hearsay evidence, rather than personal and direct inspection, inquiry, and examination of the facilities and practices criticized. It was also pointed out that some of the more sweeping recommendations called for the intervention of other Government agencies; for, in some cases, the complete remodeling of the entire health organization of a state. The question was raised as to whether this could constitute a proper field of official recommendation from the Subcommittee on Venereal Diseases in a formal

report. It was stated that a nationally known expert in the field of law enforcement within the province of venereal disease control had personally examined several of these reports, and indicated that the individuals making them would be well advised to have their attorneys at hand if material phrased as these reports are, and failing to differentiate hearsay from actual evidence, should reach the public or a litigiously-minded public official or organization. It was further pointed out that the vigor of the language employed in some instances, especially with respect to hearsay evidence, might, if the language were broadcast, imperil the good will and cooperative frame of mind which might be regarded as an essential basis for harmonious constructive action in some of the problems involved. The material might provoke anger, but with it, instead of conformity, only more obstinate opposition and indifference. It was pointed out that certain of the reports contained among the recommendations material for which it was quite impossible to hold the individual observers responsible, since they had no knowledge of either the facts or the recommendations appropriate to them. The use of hearsay, expressions of opinion, and even of editorial prerogative might be regarded as placing these reports in the category of unofficial, or at least strictly confidential report material, entirely unsuited to wide-spread or even moderately restricted circularization in its present form among state officials. It was difficult to imagine that the hotter parts of the material might not reach the press via politically minded and not too scrupulous intermediaries, and become the basis for an undesirable sensationalism and for the actual defeat of the cooperation and conformity to standards desired.

Upon inquiry by the members of the Committee as to the use which had already been made of these presumably confidential reports, it

appeared that in addition to the Surgeon General of the United States Public Health Service and Dr. Vonderlehr, the material had been available to at least seven persons in the Surgeons General's Offices of the Army and Navy. Dr. Pepper stated that all the members of his Medical Committee had received copies of the reports, and that the material had already been recognized as containing "dynamite". The Committee had not however, been specifically warned to regard these reports as strictly confidential and Dr. Pepper expressed the intention of communicating at once with each member, warning them that this material was to be held in the strictest confidence. Following this discussion it was moved and seconded that the Venereal Disease Subcommittee request that all agencies and individuals who have received copies of these reports be requested to regard them, in their present form, as strictly confidential and subject to revision by the Committee. It was requested that no further circulation of these reports be carried out until the Subcommittee has passed upon and authorized both the form and content of the material.

The discussion then turned to the use which it was expected to make of these reports, and Dr. Weed was formally asked to state the position of the Medical Sciences Division of the National Research Council, which is paraphrased as follows: it is desired that these reports be circulated to the Surgeons General of the United States Public Health Service, the Army, and the Navy, even without preliminary ratification by the Committee in order to conserve time and to make available what might properly be regarded as confidential information obtained through competent observers upon local conditions, of which these officers must have cognizance.

It was further contemplated that these reports, after modification if desired, and approval by the Subcommittee, should be circu-

lated to state officials, including governors, state public health officers and so forth, both to inform them as to conditions, and to make clear to them the points at which pressure might have to be exerted to secure conformity to practices appropriate to the emergency. Dr. Weed stated that he placed a high value upon the analysing and appraising power of an expert in a field of medical work who could rapidly and effectively, because of previous knowledge and experience, evaluate in a significant manner situations which a less experienced analyst might have to ponder for weeks and study in far greater detail. It was suggested in response to this estimate of the value of these reports that the service of an expert in this capacity could be made available, but that the estimates should be made confidentially in the first place and publicized only after careful reconsideration as to the best use that could be made of them by the body or committee assuming the responsibility for the report.

It was then requested that Dr. Usher express himself in behalf of the Public Health Service on just what this Service desired of the reports since it had provided a large part of the initiating energy and the ways and means, unofficially, for the conduct of the inspection, and Dr. Vonderlehr had already reviewed the reports in behalf of the Public Health Service.

Dr. Usher after consultation with Dr. Vonderlehr on the telephone, indicated that it was desired that the reports for issuance to the state and other authorities previously described, remain as nearly as possible in their present form, but that the Public Health Service desired that the reports adhere to provable facts and material. Dr. Usher was asked to decide whether Dr. Vonderlehr should be asked to be present in person at this point in the discussion.

It was finally agreed that the following procedure with reference to the reports should be adopted by the Committee. The reports in their present, strictly confidential, form, should be returned to their authors in order that they might revise the wording of their recommendations so as to accord with the principles elaborated in the above discussion. It was suggested that in addition to attention to the hearsay element in the collected evidence, an attempt should be made to smooth out the phraseology with a view to provoking as little needless anger and antagonism as possible. It was pointed out by Dr. Cox that reports such as these could be rendered completely edentulous if not actually emasculated by the "pulling" of necessary "punch". He repeatedly insisted that this consideration be duly regarded. Dr. Usher was then asked to state what had been the fate of the first two reports, namely on Texas and Louisiana, passed by the Committee in their practically original form. He stated that the Louisiana report had been received by the state officials at a time when a political change accomplished a large part of the purposes of the Subcommittee's recommendations, without drawing the Subcommittee too clearly into the issue. He stated that the report on the State of Texas had provoked anger without specific details, but that apparently there had been a good effect in the form of a movement in the State legislature for an increased appropriation in behalf of venereal disease control.

In order that all interests in the matter be conserved, it was made part of the recommendations of the Subcommittee that when each author had had the opportunity to review his recommendations, he become a member of an editorial committee, as a sub-committee of the Sub-committee, consisting of Dr. Vonderlehr, Dr. Clarke, and the author himself, to agree upon a final form for his recommendations

which could presumably be passed by the Subcommittee at its next meeting with relatively little controversy. The Acting Chairman thereupon named Dr. Clarke and the respective report authors to this subcommittee and requested that Dr. Usher notify Dr. Vonderlehr of the part he is requested to play in the matter.

The above being placed in the form of a motion and seconded, no dissenting voice was heard, and the motion was passed.

As the final item of business, the Acting Chairman stated that he had received from Dr. Weed a letter and other correspondence from Dr. Harold Thomas Hyman of New York City, to the Surgeon General of the United States Army, and to Captain James Gordon of the Surgeon General's Office, relative to the consideration which he, Dr. Hyman, desired to have given to the recent report by Doctors Elliott and his associates, as well as Dr. Hyman and his associates, at the Cleveland session of the American Medical Association, on the intensive treatment of syphilis commonly known as the "five-day treatment". Dr. Hyman had indicated that the decision of the Subcommittee on Venereal Diseases to recommend to the Surgeon General's offices of the Army and Navy adherence to established conservative methods might be or have been influenced by professional inertia or personal animosity.

The status of the five-day treatment, so-called, was thereupon rediscussed, by the members of the Subcommittee, and attention directed by several members to the fact that thus far no reasons had appeared for altering the original recommendations of the Subcommittee to the effect that this method of treatment must be regarded as still in the experimental stage. Dr. Clarke, a member of the board supervising the use of this treatment in certain New York hospitals, agreed that the original recommendation should still stand. It was therefore moved and seconded that the so-called intensive or five-day method,

while its usefulness under certain circumstances was freely conceded, be not as yet recommended to the Surgeons General of the Army and Navy for other use than such as might be decided upon by the Surgeons General or their authorized subordinates in charge of hospital units to whom autonomy in such matters might properly be granted, under special circumstances.

The recommendations of the Subcommittee with respect to the so-called "five-day system" remain, therefore, substantially unchanged over previous decision.

Upon the completion of this business, the Subcommittee was adjourned sine die to await the call of its Chairman or Acting Chairman, through Dr. Weed.

MINUTES OF THE NINTH MEETING OF THE SUBCOMMITTEE ON
VENEREAL DISEASES OF THE NATIONAL RESEARCH COUNCIL.

January 17, 1941.

The ninth meeting of the Subcommittee on Venereal Diseases of the National Research Council was held in Washington January 17, 1941. Present were the following members of the Subcommittee: Doctors Moore (Chairman), Stokes, Ayles, Mahoney, Cox, and Clarke; also Doctors Weed, Pepper, Larkey, and Cushing of the National Research Council; Lt. Colonels Callender, Simmons, and Kimbrough, and Capt. James H. Gordon, U. S. Army; Comdr. Stephenson, U. S. Navy, and Doctors Vonderlehr and Usher, U. S. Public Health Service.

The following recommendations were approved:

(1) The incidence of venereal disease in a given unit of the U. S. Army or Navy is not necessarily an index of lax discipline in this command, but may instead depend much more upon local conditions beyond the control of the unit commander. To place ultimate responsibility for venereal disease incidence upon the unit commander, with resultant adverse notations upon his service record or with other disciplinary action, inevitably leads to some concealment of infection by enlisted personnel, with consequent failure of infected men to receive any treatment, or treatment often inadequate, from non-official rather than from Service sources, and to an artificially low venereal disease rate. It is therefore recommended that in every instance where a high venereal disease rate continues to exist in a given command, the Corps Area Commander or his representative and the Corps Area Surgeon or his representative should investigate the reasons therefor; and that a high venereal disease rate in any command should not be interpreted as a measure of the inefficiency of the Commanding Officer, nor lead to disciplinary action of any nature against him, unless and until such investigation has confirmed neglect on the part of the Unit Commander.

(2) It is recommended that in U. S. Army and Navy hospitals the care of patients with venereal diseases of all types be concentrated as rapidly as practicable under the management of physicians with special experience in venereal diseases. This recommendation does not imply any qualifications as to the previous basic training, whether medical, dermatologic, urologic or other, of such specially trained physicians; but does imply that the diagnosis and treatment of any patient with venereal disease, and especially with syphilis of any type, is a general medical problem rather than one belonging to another limited specialty.

(3) Periodic routine serologic testing for syphilis of all personnel engaged in food-handling is an unnecessary and unduly discriminatory procedure, since the risk of male personnel acquiring syphilis from masculine food-handlers is negligible. It is therefore recommended that the periodic serologic testing of food handlers in the armed services be forthwith discontinued.

(4) It is recommended that a proposed "bill to prohibit prostitution", etc. herewith quoted, is approved by this Subcommittee:

A BILL to prohibit prostitution within such reasonable distance of military and/or naval establishments as the Secretaries of War and/or Navy shall determine to be needful to the efficiency, health, and welfare of the Army and/or Navy.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That until May fifteenth, 1945, it shall be unlawful, within such reasonable distance of any military or naval camp, station, fort, post, yard, base, cantonment, training or mobilization place as the Secretaries of War and/or Navy shall determine to be needful to the efficiency, health and welfare of the Army and/or Navy, and shall designate and publish in general orders or bulletins, to engage in prostitution or to aid or abet prostitution or to procure or solicit for the purposes of prostitution, or to keep or set up a house of ill fame, brothel, or bawdy house, or to receive any person for purposes of lewdness, assignation, or prostitution into any vehicle, conveyance, place, structure, or building, or to permit any person to remain for the purpose of lewdness, assignation, or prostitution in any vehicle, conveyance, place, structure, or building; and any person, corporation, partnership, or association violating the provisions of this chapter shall, unless otherwise punishable under the Articles of War or the Articles for the government of the Navy, be deemed

guilty of a misdemeanor and be punished by a fine of not more than \$1,000, or by imprisonment for not more than one year, or by both such fine and imprisonment, and any person subject to military or naval law violating this chapter shall be punished as provided by the Articles of War or the Articles for the government of the Navy, and the Secretaries of War and of the Navy are hereby authorized and directed to take such steps as they deem necessary to suppress and prevent the violation hereof and to accept the cooperation of the authorities of States and their counties, districts and other political subdivisions in carrying out the purposes of this Act."

(5) This Subcommittee on Venereal Diseases believes that commercialized and clandestine prostitution is an important element in the spread of venereal diseases among military and naval personnel. The incidence of such infections in the armed forces may be reduced by minimizing the opportunities for contact of such personnel with potentially infected women. These opportunities may be minimized if the local police authority will close houses of prostitution and prevent so far as possible flagrant solicitation by prostitutes. It is therefore recommended that U. S. Army and Navy through their liaison with the U. S. Public Health Service urge the adoption of such a policy of repression of prostitution upon local police authorities in areas near military or naval concentration.

(6) Furthermore, competent public health authorities have shown that periodic medical examination of prostitutes is ineffectual in detecting the presence or absence of infectious venereal disease, and is actually dangerous in that such a system of examination provides a false sense of security for prostitute and customer.

It is therefore recommended that U. S. Army and Navy, again through the liaison with the U. S. Public Health Service, advise State and local health departments that this procedure where practiced should be promptly discontinued. This recommendation does, ^{not} however, imply that epidemicologic examination of prostitutes, commercial or clandestine, when such women are named as contacts by infected military or naval personnel or civilians, should be discontinued. On the contrary, this latter policy of epidemiologic investigation should be vigorously employed and

special effort should be made to trace all sources of infection and to bring them under appropriate medical control, as outlined in previous recommendations of this committee.

(7) The reports to this Subcommittee concerning the activities of the Louisiana and Texas State Departments of Health in venereal disease control were approved by the Subcommittee. Copies of these reports have already been circulated to all members of the Subcommittee, the Chairman of the Committee on Medicine, the Director of the Division of Medical Sciences, and to the U. S. Army Navy, and Public Health Service officers associated with the Subcommittee.

It was moved and carried that these reports on Texas and Louisiana be transmitted through the Chairman, Division of Medical Sciences, National Research Council, to the Health and Medical Committee, Federal Security Agency, with the request that, if approved by this latter Committee, copies of each report be forwarded to the Governor of the State and the State Health Officer in question, to the Surgeons General of the U. S. Public Health Service, Army, and Navy, and to the Chief, Children's Bureau.

* * * * *

There was next considered the risk of the use of syphilitic blood for transfusion from blood or plasma banks. It was decided that inadequate information on this topic was as yet available and that the question be referred to the Committee on Blood Substitutes with the suggestion that further experimental work be undertaken. A letter has accordingly been written by your Chairman to Dr. C. C. Sturgis, Chairman of the Subcommittee on Blood Substitutes, as follows:-

"Dear Dr. Sturgis:

At a meeting of the Subcommittee on Venereal Diseases of the National Research Council on January 17, there was considered the possible risk of use of syphilitic blood for transfusion from blood or plasma banks. The following statement was submitted for consideration by my committee:-

'Though every effort should be made to avoid the use of syphilitic blood for transfusion, by means of history, physical examination, and routine serologic testing of all donors, nevertheless and in spite of all such precautions, a syphilitic donor may be inadvertently selected. The risk of transmission of syphilis to the recipient may be completely avoided if all blood or plasma used for transfusion is stored at icebox temperature (4° C.) for a minimum of 96 hours before use.'

"After some discussion by members of my committee, it was brought out that experiments in the laboratories of Drs. Chesnoy and Turner at the Johns Hopkins had shown that while blood heavily seeded with spirochetes was non-infectious for animals after storage under blood bank conditions for 72 hours. It was felt, however, that no information was available as to the possible infectiousness of plasma prepared from stored whole blood, frozen at -80° C. and dried in vacuo while frozen. It is of course known that the T. pallidum will live indefinitely in material frozen at -70° to 80° C. while it will not survive in a temperature range of -25 to +4° C. It is also known that the treponemes will not survive drying at room temperature. It is not, however, known whether treponemes will survive a preliminary freezing at -70 to 80° C. followed by drying.

"My committee felt that further consideration of this problem should be referred to your committee, and that planned experiments covering the point might be desirable in view of the inadvertent inclusion among prospective donors of certain seronegative but nevertheless infectious syphilitics.

"I shall appreciate it if you will notify me of whatever action may be taken by your committee on this point."

There was next briefly discussed the Librale Section of the Adjutant General's Office, U. S. Army, and the place of civilian welfare organizations in the venereal disease control program. It was pointed out that a Committee on Education, Recreation and Community Service had been appointed by the War Department under the chairmanship of Mr. Frederick Kl Osborne. The chairman, Subcommittee on Venereal Diseases, was authorized to obtain an appointment with Mr. Osborne to discuss the role of substitutive activities in the control of venereal disease with him and to report back to the Subcommittee at a subsequent meeting.

The chemotherapeutic recommendations as to yaws and pinto, to be prepared by Comdr. Stephenson, were not yet available and will be considered at a subsequent meeting.

There ensued finally a discussion as to the value of this Subcommittee to the armed services. Col. Simmons and Comdr. Stephenson expressed the thanks of the Surgeons General, U. S. Army and Navy, for the work of this Subcommittee. Both Col. Simmons and Comdr. Stephenson stated that they were prepared to offer an informal discussion of the approval or disapproval of the recommendations of this Subcommittee by the U. S. Army and Navy, respectively, but that this discussion would require so much time as to necessitate its postponement to another meeting. Dr. Wood reported on the action taken concerning certain recommendations of this Subcommittee by the Committee on Health and Medicine, Federal Security Agency. As a result of this general discussion it was moved and carried that this Subcommittee express its appreciation of the thanks conveyed to us by the Surgeons General, U. S. Army and Navy, and also to express our willingness to continue serving in any capacity required of us. Furthermore, it was moved and carried that this Subcommittee would be gratified if at subsequent meetings we could be kept informed by Army and Navy of their consideration of the recommendations submitted.

The meeting then adjourned.

J. E. Moore, M.D.
Chairman.

8

Minutes of the Eighth Meeting of the Subcommittee on Venereal Diseases
of the
National Research Council.

September 20, 1940.

On September 20, 1940, there was held at the National Research Council in Washington, D. C., the eighth meeting of the Subcommittee on Venereal Diseases of the Committee on Chemotherapeutics and Other Agents. Present were:- Dr. J. E. Moore, Chairman; Drs. Oscar Cox, John H. Stokes, Edwin Alyea, and Walter Clarke, members of the Committee; and the following others:- Drs. Perrin Long and Sanford Larkey, Colonels Callender, Kimbrough, and Leon Fox, all of the U. S. Army Medical Corps; Commander Charles S. Stephenson, U. S. Army Medical Corps; and Dr. Glen Usher, U. S. Public Health Service.

The Committee proceeded with further consideration of the Chairman's Memorandum of Aug. 30, 1940.

1. There was first discussed the question of the management at demobilization or discharge of military and naval personnel infected with syphilis.

The Committee adopted as a recommendation certain instructions prepared by Dr. Stokes and amended in Committee, to be prepared by Dr. Stokes in final form and later to be appended to these Minutes as Exhibit A.

2. The previously adopted recommendation as to punitive measures for venereal disease control, which appears as lines 4 to 8, page 5, of the Minutes of the Sixth Meeting, as lines 9 to 14, Chairman's Memorandum of Aug. 30, 1940, and as lines 11 to 15, Minutes of the Seventh Meeting, was amended; and in its final recommended form reads as follows:-

"In order to further the control of the venereal diseases, all provisions relating to forfeiture of pay and/or loss of time in U.S. Army, Navy, Coast Guard, and Public Health Service personnel infected with any venereal disease, whether or not such personnel is therefore absent from duty, and whether such disease was contracted at any time before or after entry into the Services, should be forthwith repealed."

3. It was recommended that the U. S. Army and Navy adopt a uniform diagnostic nomenclature as to syphilis, to replace the widely different nomenclatures now in use; and that the Memorandum of August 9, 1940 prepared by the Chairman, as amended by the Committee, and herewith appended to these Minutes as Exhibit B, be utilized for this purpose.

4. Memoranda concerning yaws and pinta designed for ultimate inclusion by the Committee on Chemotherapeutics and Other Agents with similar Memoranda on infectious disease, were considered by the Committee and not agreed upon.

Commander Stephenson was delegated to prepare new versions of these Memoranda as to yaws and pinta, which will be circulated among Committee members for final approval and adoption as recommendations.

5. It was recommended that Circular Letter No. 1, Compilation of Circular Letters, S. G. O. January 2, 1940, Section 29, paragraphs C (3) and (4) be amended to read as follows:-

"(3) Period of observation:- On the completion of the optimum treatment outlined in paragraph b above, the patient will be kept under observation for five years, or for such part of this time during which he remains in the Service. During the first year, blood tests will be done at intervals of approximately one month. Careful physical examination will be made after approximately six months of observation and at the end of the year. This latter examination will include an examination of the spinal fluid and an X-ray or fluoroscopic examination of the heart and great vessels. If no evidence of activity of the infection is revealed during this year of observation, the patient will be followed for 4 additional years, with blood tests every 6 months during this period, and with yearly periodic physical examinations, these data to be added to the "Syphilis Treatment Sheet". In the event that the individual is separated from the Service before the 5 years of observation have terminated, he will be provided with the clinical features of his case required by Section II, Circular No. 60, War Department, September 10, 1937; a copy of this summary will be incorporated in the Medical record;

and he will be advised to continue these periodic examinations at the hands of a civilian physician or clinic.

"(4) A flocculation test (preferably the Eagle) will be used in evaluating the efficacy of treatment and will be requested routinely in all treatment cases. This test will be done before treatment and at the beginning and end of each course of an arsenical. Quantitative serologic tests are unnecessary in following routine treatment results and should not be requested for this purpose."

Note:- this amendment of paragraph (4) relaxes the present requirement that quantitative serologic tests shall be performed in following routine treatment results. This requirement is unnecessary for the purpose advised, and imposes an undue burden on the laboratory service.

6. Section 30, Circular Letter No. 1, Compilation of Circular Letters S. G. O. January 2, 1940, deals with the management of syphilis among enrollees of the Civilian Conservation Corps. It appears that certain administrative details in this respect are under the jurisdiction of the Social Security Director, and medical details in the jurisdiction of the U. S. Army Medical Corps.

It was therefore recommended that the Health and Medical Committee of the National Defense Council request the Federal Social Security Director and the Surgeon General, U. S. Army, to modify present procedure as to venereal diseases in C. C. C. in the following respects:-

(a) In general, the diagnostic, treatment, and public health measures for the control of venereal diseases (especially syphilis and gonorrhea) which are within the jurisdiction of the Medical Corps, U. S. Army, shall conform in all respects to the standard procedure of the U. S. Army.

Note:- This recommendation, if adopted by the Surgeon General, U. S. Army, will replace all of Section 30, Circular Letter, No 1.

(b) All applicants for enrollment in the C.C.C., already obviously infected with any venereal disease, shall be accepted for enrollment and placed under immediate treatment, unless actually physically incapacitated by such disease.

(c) All applicants for enrollment in the C.C.C., shall be subjected at the time of enrollment, to a routine serologic test for syphilis. If such test is positive, the applicant shall nevertheless be accepted for enrollment unless he is actually physically incapacitated.

(d) Any C.C.C. enrollee, infected with any venereal disease during his term of enrollment, shall not be discharged for this cause, but shall be retained in the C.C.C. and treated for such disease during such period of his enrollment as may be necessary.

(e) On discharge of any C.C.C. enrollee infected with syphilis, or with any other venereal disease still requiring further treatment, the Medical Officer in charge shall forthwith report the name, address, and diagnosis of the infected enrollee to the State Health Department of the enrollee's designated residence, together with such other data and in such manner as is proscribed for the U.S. Army.

Note: The acceptance of the recommendations in paragraphs (b), (c), and (d) above by the Federal Social Security Director, will require a radical departure from present rulings in these respects.

7. Section 31, Circular Letter No. 1, S.G.O, January 2, 1940, will require complete rewriting if and when the Surgeon General, U.S. Army, accepts a previous recommendation to substitute the Eagle for the Kahn flocculation test.

8. It was recommended that U.S. Army and Navy adopt standard record forms for the diagnosis and treatment of gonorrhoea in male and female, and of syphilis, the latter to replace the present "Syphilis Register". Copies of these records will be later appended to these Minutes as Exhibits C and D.

9. It was recommended that as a valuable measure for the maintenance of morale, the provision of normal opportunities for social contact of military, naval, and industrial personnel with the opposite sex, and the prevention of the venereal diseases, the Health and Medical Committee of the National Defense Council be requested to ask appropriate civilian welfare organizations promptly to establish, in suitable areas of military and naval concentration, in contiguous cities.

and in centers of industrial concentration, recreation huts adequately staffed with personable women of comparable age groups to those of the military, naval, and industrial personnel involved.

10. The question of personnel was further considered. The Chairman read a letter of Sept. 17, 1940, from himself to Col. C.C.Hillman, drawing attention to the fact that certain officers already members of the Medical Reserve Corps or National Guard are specially qualified in venereal disease control. In order to identify those officers, it was agreed that the personnel lists of physicians specially qualified in venereal disease control, now in preparation by this Subcommittee for transmission to the Committee on Medical Preparedness of the American Medical Association, should be forwarded in duplicate to Col. Hillman and Comdr. Stephenson, for transmissal to their respective personnel officers.

11. The following motion was proposed and carried:-

"It is the sense of the Subcommittee on Venereal Diseases that its work would be facilitated if its recommendations dealing with administrative measures could be transmitted directly by its Chairman through the Division of Medical Sciences to the Health and Medical Committee of the National Defense Council without further discussion or approval by the Committees on Chemotherapeutics and Other Agents or on General Medicine; while its recommendations as to therapeutic procedures should continue to follow channels through these two latter Committees."

12. The Subcommittee then adjourned to meet again on the call of the Chairman.

J.E.Moore, M.D., Chairman,
Subcommittee on Venereal Diseases
of the Committee on Chemotherapeutics
and Other Agents.

804 Medical Arts Building
Baltimore, Maryland

October 19, 1940

To all Members of the Subcommittee on Venereal Diseases
Committee on Chemotherapeutic and Other Agents, N. R. C.
The Committee on Medicine of
The National Research Council

Dear Doctor

Enclosed herewith are copies of the proposed new history forms
for syphilis (labeled Exhibit "D" in the Minutes of the Eighth meeting
of the Subcommittee on Venereal Diseases) and for gonorrhoea (labeled Ex-
hibit "C").

These exhibits complete the roster of those referred to in
the Minutes of the Eighth Meeting.

Sincerely yours,

J. E. Moore
J. E. Moore, M.D., Chairman
Subcommittee on Venereal Diseases
National Research Council.

Cc: Dr. Alyea
Dr. Clarke
Dr. Cox
Dr. Mahoney
Dr. Stokes
Dr. Long
Comdr. Stephenson
Lt. Col. Simmons
Col. Hillman
Col. Gellender
Dr. Vonderlehr
Dr. Larkey
Dr. Wilder
Dr. Fulton
Dr. Farran
Dr. Blake
Dr. Leckwood
Dr. Marshall
Dr. Bloomfield
Dr. Bruce
Dr. Lee
Dr. Langoepe

Dr. Morgan
Dr. Palmer
Dr. Poullin
Dr. Pepper
Col. Pfeil.

Venereal Diseases

New History forms for Syphilis

GONORRHEA (FEMALE)

Serial Number	Last Name	First Name	Middle Name	Admission Date
Rate		Station		
Work (specify)				
Age	White <input type="checkbox"/>	Colored <input type="checkbox"/>	Married <input type="checkbox"/> Single <input type="checkbox"/>	Length of Service

PREVIOUS GONORRHEA

No Yes Complication (specify) _____

Date L.M.P. _____

PRESENT INFECTION

Date exposed _____ Name of Contact _____ Address of Contact _____

PREVIOUS TREATMENT THIS INFECTION

No Yes Specify _____

PHYSICAL EXAMINATION (ADMISSION)

	Normal	Abnormal
Urethra	<input type="checkbox"/>	<input type="checkbox"/>
Skene's Glands	<input type="checkbox"/>	<input type="checkbox"/>
Bartholin's Glands	<input type="checkbox"/>	<input type="checkbox"/>
Cervix	<input type="checkbox"/>	<input type="checkbox"/>
Uterus	<input type="checkbox"/>	<input type="checkbox"/>
Rt. Adnexa	<input type="checkbox"/>	<input type="checkbox"/>
Lt. Adnexa	<input type="checkbox"/>	<input type="checkbox"/>
Pelvic Peritoneum	<input type="checkbox"/>	<input type="checkbox"/>
Rectum	<input type="checkbox"/>	<input type="checkbox"/>
Joints	<input type="checkbox"/>	<input type="checkbox"/>
Lymphatic Glands	<input type="checkbox"/>	<input type="checkbox"/>

DIAGNOSIS (ADMISSION)

Gonococcus Infection
(specify location)

Blood Test for Syphilis

	Positive	Negative
Admission	<input type="checkbox"/>	<input type="checkbox"/>
Three months after admission	<input type="checkbox"/>	<input type="checkbox"/>

Officer's Signature

Rank

Menstruation (a)			
(c)	Discharge	Urethra	
		Cervix	
Tests (c)	Bartholinitis		
	Pelvic pain		
	P.I.D. Rt.		
	P.I.D. Lt.		
Smear	Gul de sec abscess		
	Urethra		
	Cervix		
	Rectum		
GC.	Urethra		
	Cervix		
	Culture		
	Rectum		
Treatment (d)	Oral		
	Local		
Reaction (f)			

(a)	(b)	(c)	(d)	(e)	(f)
Menstruation +Yes -No P-Pregnant	Signs & Symptoms 0-None 1-Slight or scanty 2-Moderate 3-Moderate or mod. profuse 4-Severe or profuse	Tests +Positive -Negative	Drugs S1-Sulfanilamide S2-Sulfapyridine S3-Sulfathiazole Etc.	Treatment SB-Sitz bath IC-Ice bag K-KMNO ₄ MAG-Mild silver proteinate AC-Actual cautery ED-Bed D-Douche AG-AGNO ₃ SAG-Strong silver proteinate ES-Electro-surgery	Reactions M-Mild S-Severe F-Fatal 1-Blood 2-Nervous System 3-Skin 4-G.I. 5-Febrile 6-Kidney

Codes

PROBATION AND DISPOSAL

Quarterly Re-check		
Date	Serol.	Done by
I		CSF
II		
III		
IV		

Clip hereto memo of pos. phys. find.
 Disposal
 Transferred to center

Dischg. as cured
 Dischg. to probation
 Dischg. to civil authority

Lapsed
 Died (cause, date)

SYPHILIS TREATMENT SHEET

Administrative Data
for Army or Navy
Here

INSTRUCTIONS

Use ink or indelible pencil if possible. Give the treatment indicated by each ~~letter~~ at the time indicated. Record irregular treatment by the week given. For lapse enter (L). Reference numbers indicate following: (1) Drug letters: AO (arsenoxide); AB (arsphenamine); NE (neosalvarsamine). If other arsenical place abbreviation here
 (2) Bi salicylate, enter as SAL. Other abbreviation here
 (3) Dose for AO in milligrams, others in decigrams. (4) Record as reported (Eagle test). (5) Record under CSF column as N (negative), Grade I, II, III. See manual if positive. Record full findings below.

DATE	WEC	Protein test	Compl. Fixa.	COLLOIDAL

WEEK	DATE	DRUG EARLY LATENT As Bi Ac Bi	INJ. NO. As Bi	SEROL TEST	REACTION OR COMMENT	5 C S F	6 C S F
1		X					
2		X		XE			
3		X					
4		X					
5		X					
6		X					
7		X					
8		X		XE			
9		X					
10		X		XL			
11		X					
12		X					XE

The designations 'E' or 'L' refer to early and latent Syphilis respectively.

WEEK	LATE	DRUG				INJ. NO.	DOSE	SEROL. TEST	REACTION OR COMMENT	C S F
		EARLY		LATENT						
		As	Bi	As	Bi					
25	X	X		X						
26		X		X						
27		X		X						
28		X		X						
29		X		X						
30		X		X						
31		X	X	X						
32		X	X	X						
33		X	X	X						
34		X	X	X						
35		X	X	X						
36		X	X	X						
37		X	X	X						
38		X	X	X						
39		X	X	X						
40		X	X	X						
41		X	X	X						
42		X	X	X						
43		X	X	X						
44		X	X	X						
45		X	X	X						
46		X	X	X						
47		X	X	X						
48		X	X	X						

P
E
S
T

Note: Continue 10 injection Bi courses in alternation with 8 weeks rest periods to total of 60 injections using new sheet and inserting correct numbers for weeks.

GONORRHEA (FEMALE)

Serial Number	Last Name	First Name	Middle Name	Admission Date
Rate		Station		
Work (specify)				
Age	White <input type="checkbox"/>	Colored <input type="checkbox"/>	Married <input type="checkbox"/>	Single <input type="checkbox"/>
Length of Service				

PREVIOUS GONORRHEA

No Yes Complication (specify) _____

Date L.M.P. _____

PRESENT INFECTION

Date exposed _____ Name of Contact _____ Address of Contact _____

PREVIOUS TREATMENT THIS INFECTION

No Yes Specify _____

PHYSICAL EXAMINATION (ADMISSION)

	Normal	Abnormal
Urethra	<input type="checkbox"/>	<input type="checkbox"/>
Skene's Glands	<input type="checkbox"/>	<input type="checkbox"/>
Bartholin's Glands	<input type="checkbox"/>	<input type="checkbox"/>
Cervix	<input type="checkbox"/>	<input type="checkbox"/>
Uterus	<input type="checkbox"/>	<input type="checkbox"/>
Rt. Adnexa	<input type="checkbox"/>	<input type="checkbox"/>
Lt. Adnexa	<input type="checkbox"/>	<input type="checkbox"/>
Pelvic Peritoneum	<input type="checkbox"/>	<input type="checkbox"/>
Rectum	<input type="checkbox"/>	<input type="checkbox"/>
Joints	<input type="checkbox"/>	<input type="checkbox"/>
Lymphatic Glands	<input type="checkbox"/>	<input type="checkbox"/>

DIAGNOSIS (ADMISSION)

Gonococcus Infection
(specify location)

Blood Test for Syphilis

	Positive	Negative
Admission	<input type="checkbox"/>	<input type="checkbox"/>
Three months after admission	<input type="checkbox"/>	<input type="checkbox"/>

Officer's Signature _____

Rank _____

MINUTES OF THE SEVENTH MEETING OF THE SUBCOMMITTEE ON VENEREAL

DISEASES OF THE NATIONAL RESEARCH COUNCIL

September 6, 1940.

On September 6, 1940, there was held at the National Research Council in Washington, D.C., the seventh meeting of the Subcommittee on Venereal Diseases of the Committee on Chemotherapeutics and Other Agents. Present were Dr. J.E. Moore, Chairman of the Committee, Dr. Oscar Cox, Dr. Edwin Alyea, Dr. John K. Stokes, Dr. John F. Mahoney, Dr. Walter Clarke, and also the following others: Dr. Lewis Weed, Dr. Sanford Larkey, Dr. Russell Wilder, Dr. John F. Fulton, Colonels Callender, Kimbrough and Simmons, Major F. B. Wakeman, all of the U.S. Army Medical Corps, Comdr. C. S. Stephenson, U. S. Navy Medical Corps, and Dr. R. A. Vonderlehr, Assistant Surgeon General, U.S. Public Health Service.

The Committee proceeded with a consideration of the lengthy memorandum of August 30, 1940, which has already been circularized.

It was reported that the problem of experimentation with sulfonamid compounds on muscular coordination has already been referred to the Subcommittee on Clinical Investigation of the Committee on Medicine, and by this Subcommittee to Dr. E. K. Marshall, Jr., Johns Hopkins University.

On the question of training of Service Medical Officers a memorandum was submitted, a revision of which is herewith incorporated.

* * * * *

The Subcommittee on Venereal Diseases of the National Research Council has already recommended that special training in venereal diseases be made available for Army and Navy Medical Corps, and that these Corps assign Officers as practicable for such training in two categories, as follows:-

1. A group of Officers for each Service in the proportion of at least one such Officer for every 50,000 strength, to act as instructors and consultants,

if necessary, to unit Medical Officers. These consultant officers should have at least 6 months' intensive training; and for the purpose of the following discussion may be designated as "long-term trainees". With the proposed and shortly to be authorized expansion of the Army to about 1,200,000 the Army Medical Corps should possess approximately 25 such officers.

2. Junior (unit) Medical Officers of both Services, but especially Army, should receive short training courses, approximately two weeks in duration. These may be designated as "short-term trainees".

* * * * *

With the passage by Congress of the bill authorizing the President to mobilize the National Guard and the Officers' Reserve, it seems certain that the shortage of medical officers in the two Corps will be promptly relieved, and that officers from each Service will be available for detail to such training.

* * * * *

It is obvious that long-term training should be carried out, at least for the present, in civilian university training centers which (a) have at their disposal adequate laboratory and clinical facilities, and (b) have already accumulated experience in this type of postgraduate teaching by previous cooperation with the U. S. Public Health Service.

As to short-term training, there was held at the September 6, 1940, meeting of the Subcommittee a discussion as to whether this type of training might be more suitably offered in (a) civilian university training centers, as above, or (b) by traveling groups of civilian or Service instructors who might go periodically to Army cantonments or troop or naval concentration centers. The consensus of the Subcommittee was that the assignment of Service Officers to civilian university training centers was by far the preferable of these two alternatives.

* * * * *

The Chairman of your Subcommittee has investigated the available facilities for these two types of training and submits the following information:

Long-term training facilities:- These are already available at

Johns Hopkins University, Baltimore, Md.
University of Pennsylvania, Philadelphia, Pa.
New York University, New York, N.Y.
University of Michigan, Ann Arbor, Mich.

Each of these institutions now has organized, or could readily organize, training programs requiring 6-8 months for completion, in which the trainees could receive practical instruction in the clinical and public health aspects of the several venereal diseases, adequate to permit the trainees to function as instructors and consultants to Junior Medical Officers.

The Johns Hopkins University could accept 6 such trainees at once; the University of Pennsylvania could accept 2.

Information is not available as to the numbers of long-term trainees acceptable to New York University or the University of Michigan; but it is assumed that each institution could also accept 6 trainees (a total of 20).

In each case, the Universities would prefer to have trainees assigned as of the beginning of the academic year (about October 1); but could probably accept them at any time.

No additional funds would be required for this purpose by the Johns Hopkins University or the University of Pennsylvania. Further information and conference would be required by New York University and the University of Michigan.

Short-term training facilities:- Two weeks' training courses, with a more or less uniform curriculum, including from 70 - 90 hours of practical and didactic work, are already available, or could be readily organized, at the following institutions:-

University of Michigan, Ann Arbor, Mich.
Leland Stanford Jr. University, San Francisco, Calif.
New York University, New York, N.Y.

University of Pennsylvania, Philadelphia, Pa.
 Louisiana State University, New Orleans, La.
 Harvard University, Boston, Mass.
 Vanderbilt University, Nashville, Tenn.
 Hot Springs Medical Center (U.S.P.H.S.) Hot Springs, Ark.
 Howard University (Negro physicians), Washington, D.C.

and probably also, if desired, at

Duke University, Durham, N.C.
 University of North Carolina, Chapel Hill, N.C. (not before 1-1-41)

Such courses could be started in each institution immediately (with 2 weeks' advance notice).

Trainees could be accepted in the following numbers, assuming that courses were repeated monthly:

	<u>Limit of each group</u>	<u>Total number per year</u>	<u>Course could be given</u>
University of Michigan	25	300	12 times yearly
Leland Stanford	10	50	5 times yearly
New York University	10	120	12 times yearly
University of Pennsylvania	5	25	5 times yearly
Louisiana State University	25	300	12 times yearly
Harvard University	10	120	12 times yearly
Vanderbilt University	8	48	6 times yearly
U.S.P.H.S. Center, Hot Springs	25	650	Continuously
Howard University	8	160	Continuously

Data on these points are not yet available from the University of North Carolina or Duke.

Additional funds would not be required by the Universities of Pennsylvania, Duke, or Louisiana State.

Some addition to present budgets, amounts to be determined by conference, would probably be required by the Universities of Michigan, Stanford, and New York.

Harvard University would require about \$9,000.00 per year; Howard about \$12,600.00; Vanderbilt \$4,320.00; North Carolina \$3,450.00;

Hot Springs requires 2 additional instructors, which the U. S. Public Health Service will furnish immediately if arrangements are completed for this use of its Medical Center.

* * * * *

Tuition and registration fees have already been waived, or arrangements

long and short-term training.

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In the light of this information the Subcommittee adopted as a formal recommendation the following:

If the expansion of the Medical Corps of the two Services permits, and if and when Congress has authorized and appropriated the funds necessary to permit the training of Army and Navy Medical Officers in civilian institutions:

1. That not to exceed 6 long-term trainees be assigned at once from among the regular Officers of the Services to the Johns Hopkins University for a period not to exceed 8 months; and that negotiations be initiated at once through the Offices of the Surgeons General of the two Services with the University of Pennsylvania, New York University, and the University of Michigan as to the maximum number of long-term trainees immediately acceptable to them; and that Officers be assigned to these institutions for training of similar character and duration in such numbers as may be necessary and feasible.

2. That for the present short-term (2 weeks) training facilities be limited to the Universities of Michigan, Pennsylvania, New York, Duke, Louisiana State, and the U.S. Public Health Service Medical Center at Hot Springs, as being immediately organized to proceed with such training with little or no additional expense; and that unit (especially Junior) Medical Officers of each Service be assigned for such training in rotation in those numbers which seem necessary and feasible to the Surgeons General of each Corps.

3. That negotiations continue through the Offices of the Surgeons General of the two Services and/or through the Chairman, Division of Medical Sciences, National Research Council, with the appropriate Committee of the Association of

American Medical Colleges for the development of such short-term training facilities, if necessary, at the Universities of Leland Stanford, Harvard, Vanderbilt, North Carolina, Howard, Southern California, Oregon, Emory, the Mayo Clinic, or others.

4. That as an alternative, but much less desirable proposal, and especially pending the availability of the training facilities described above, the possibility be explored through the Surgeons General of the two Services with the staffs of civilian universities or Public Health Service training centers, of providing short-term training facilities at Army and Navy Medical Centers or in areas of troop and Naval concentrations through the utilization of traveling groups of civilian instructors.

* * * * *

With reference to the already adopted recommendation that "all provisions relating to forfeiture of pay in the two Services in infected and military personnel, whether or not in absence from duty, and whether the disease was acquired at any time before or after entry into the Services, be forthwith repealed", it was further recommended:

That the Legal Department of the American Social Hygiene Association be requested to draw up a bill embodying the above recommendation; that this bill be discussed by Dr. William A. Snow of the American Social Hygiene Association with the Surgeons General of Army, Navy, and U. S. Public Health Service, and with the Secretaries of War and Navy, and the Social Security Director, and with other Officers of the three Services, as may be necessary preliminary to its possible refer through the National Defense Council to the Chairmen of the appropriate committees of the House of Representatives and Senate.

The inclusion of the U. S. Public Health Service in this further recommendation is based on the fact, as pointed out by Dr. Vonderlohr and others, that the provisions for forfeiture of pay apply also to the U. S. Public Health Service, particularly the U. S. Coast Guard, which should be included in the proposal as a whole.

Concerning the long recommendation as to the cooperation of the Army and

Navy with the civilian health authorities in the control of the venereal diseases, the Chairman read the Subcommittee a letter from Dr. Vonderlehr announcing his intention of publishing in Venereal Disease Information certain excerpts from this recommendation. This led to a general discussion of the question of publication of the deliberations of this Subcommittee. It was agreed that a summary of these deliberations, together with the specific recommendations of the Subcommittee, would be prepared for joint publication, if this can be arranged, in the Journal of the American Medical Association and in Venereal Disease Information. Dr. Vonderlehr agreed to publish the entire summary as a supplement to Venereal Disease Information, if so much space was required.

It was agreed that the previously adopted recommendation "that all antigens for serodiagnostic tests for syphilis sold in interstate commerce, be brought under the supervision of the Biologic Control Act", should be referred to the Surgeon General of the U. S. Public Health Service and, through him if approved, to the Chairmen of the appropriate committees of Senate and House of Representatives.

It was further recommended that all arsenical drugs now or in the future, used in the treatment of syphilis, should be brought under the supervision of the Biologic Control Act.

With regard to the examination of enrollees for enlistment, and as to the eligibility for service of such persons, it was recommended that enrollees in Army and Navy, whether volunteers or selective service, if infected with any venereal disease, be accepted for enrollment unless such enrollee is actually or potentially physically incapacitated by such disease.

It was moved and carried that this Subcommittee prepare a list of personnel specially trained in the venereal diseases for submission to the Committee on Medical Preparedness of the American Medical Association, with the request that these data be entered on the punch card information of the individuals named for the ultimate use of Army and Navy Medical Corps.

The Chairman presented to the Subcommittee certain correspondence between Dr. Weed and Dr. Farran indicating the desire of the Public Health Service that the Subcommittee on Venereal Diseases should consider the methods employed in some of the state-wide programs of venereal disease control which have special importance to national defense; and that in particular these programs be examined in the near future in the following states: Louisiana, Texas, Kansas, Missouri, and Nebraska. It was moved and carried that the Chairman of the Subcommittee be authorized to make such surveys, and if necessary or desirable, that he be authorized to associate with himself other observers; that he report back his findings to the Subcommittee; and that after approval by the Subcommittee, the recommendations be transmitted to the Surgeon General of the U. S. Public Health Service.

The Chairman presented to the Subcommittee a letter from Dr. William P. Boardman, Boston City Hospital, offering the facilities of his clinic and WPA project for the accomplishment of research problems in syphilis to be suggested by the Subcommittee on Venereal Diseases. The Chairman was authorized to reply to Dr. Boardman that at the moment the Subcommittee had no projects to propose which seemed suitable, and to thank him for his offer.

Dr. Vonderlehr requested the advice of the Subcommittee on a proposal that routine serologic tests for syphilis be made available on a volunteer basis to the 16,500,000 men available for registration under the Selective Service Act. He pointed out that while not all registrants would volunteer, nevertheless a considerable proportion would probably do so, and that the project offered an unparalleled opportunity to discover a great deal of previously undetected syphilitic infection among an age group likely to be in the most communicable period of the disease. He pointed out further that, while treatment facilities are probably not available for the large number of syphilitic persons expected to be discovered, nevertheless the need for such treatment facilities brought out by this survey would be a valuable argument for the appropriation of additional public funds to the extent appar-

ently required. As to the feasibility of the survey, Dr. Vonderlehr reported that with the approval of the U. S. Army and Navy, the U. S. Public Health Service would request the cooperation of the American Medical Association, State and local Health Departments, and other volunteer agencies to set up blood testing teams at all important registration points, to provide for the examination of those specimens through State and local Health Department laboratories, and to report the results either directly to the registrant or to a physician or medical agency to be designated by him.

The Subcommittee agreed that, if this suggestion could be carried out, it would constitute a syphilis survey on a hitherto unattainable scale. It was therefore recommended that if, after consultation between appropriate Officers of Army, Navy, and Public Health Service, this plan proves administratively feasible, it be put into immediate effect.

The meeting then adjourned.

MINUTES OF THE SIXTH MEETING OF THE SUBCOMMITTEE ON VENEREAL DISEASES
OF THE NATIONAL RESEARCH COUNCIL

July 19, 1940

The sixth meeting of the Subcommittee on Venereal Diseases of the Committee on Chemotherapeutics and Allied Subjects of the National Research Council was held in Washington on Friday, July 19. Present were Dr. J. E. Moore, Chairman of the Committee, the following members of the Committee:- Dr. Osoar Cox, Dr. Edwin Alyea, Dr. John F. Mahoney, and Dr. Walter Clarke; Dr. Perrin Long, Chairman of the Committee on Chemotherapeutics; and the following guests:- Dr. R. A. Vonderlehr and Dr. Robert Onstott, U. S. Public Health Service; Col. J. C. Kimbrough, Col. George R. Callender, and Col. James Simmons, U. S. Army; Comdr. Charles Stephenson, U. S. Navy, and Dr. Sanford Larkey of the Committee on Information of the National Research Council.

The gonorrhea history forms for male and female, devised by the U. S. Public Health Service and the American Neisserian Medical Society, and previously recommended for adoption by the U. S. Army and Navy at an earlier meeting of this Subcommittee, were further considered. It was agreed that Dr. Cox would work out an adaptation and revision of these forms for use by the armed Services in connection with a representative of the International Business Machines Company.

These forms for gonorrhea and the history forms for syphilis previously submitted by Dr. Stokes and recommended for adoption by the Subcommittee, will be resubmitted in final form at a subsequent meeting of the Subcommittee.

On the question of the relationship between civil and military and naval medical and health authorities discussed at the last meeting, Dr. Clarke submitted a Memorandum which with slight modification was adopted by the Subcommittee as a Recommendation. This Memorandum should follow, in chronological order, the previous Recommendation of the Committee at its second meeting, which is incorporated in the minutes of the first meeting, on page 4, fourth paragraph; and ending, "to rally

and organize public support to this same end". The preamble of Dr. Clarke's Memorandum should be incorporated in the Recommendation. The Memorandum and Recommendation follow:

Both civil health authorities and military and naval medical officers should accept responsibility for the maintenance of effective liaison between their respective services in every jurisdiction where they coexist. In this interrelationship the established general principles of control of communicable diseases, not excepting syphilis, gonorrhoea and other venereal diseases so-called, should be followed. The fact that in venereal diseases the sources of infection of military and naval personnel are nearly always in the civil communities gives great importance to cooperation especially in case-finding efforts.

The Army and Navy medical Services are subject to their own respective regulations and policies and to the federal laws. Civil health authorities are subject to state laws, regulations of state (and, in a few instances, local) sanitary codes and to local ordinances not in conflict with state laws or regulations. Court decisions, if any, must always be considered in applying any public health law, sanitary code regulations, and city ordinance.

On the military and naval reservations of the United States, state public health laws and regulations and local ordinances are not operative and the medical officers of the Army and Navy are not legally bound to conform to these laws, regulations, and ordinances unless required by Army and Navy orders to do so. Army regulations (40-1080, paragraph 6) require medical officers of the Army to report to the appropriate civil health authority all cases of infectious diseases which are reportable under civil laws and regulations and to acquaint themselves with civil public health laws and regulations. This gives an official basis for highly valuable cooperation between the Army medical Services and the civil health authorities in controlling venereal diseases. It is desirable that the Navy should establish

similar regulations.

As a matter of good public health practice, cooperation should go much further. The medical officers of the Army and Navy should not only report new cases of syphilis and gonorrhoea to the appropriate civil health authorities but should also report, if possible, the known contacts to the civil health authorities in whose jurisdictions the known contacts reside. Where venereal disease control measures are most highly developed, these practices of collaboration give excellent results without friction or embarrassment to military, naval or civil authorities.

The powers and duties usually conferred upon civil health authorities can be of great assistance to this cooperative effort of civil and military and naval health and medical Services. The laws and regulations include all or most of the following:

1. Laws giving power to health departments to make regulations.
2. Laws or regulations requiring venereal diseases to be reported by physicians and others.
3. Laws giving health departments power to examine or to cause to be examined all persons who, there being reasonable grounds to believe, are infected with a venereal disease and are likely to spread their infection (mainly applied to prostitutes and other promiscuous persons).
4. Laws authorizing health officers to require infectious persons to be treated.
5. Laws and regulations authorizing and defining the isolation or quarantine of infectious individuals.
6. Laws and regulations penalizing an infected individual for knowingly infecting another with or exposing another to his infection.
7. Laws prohibiting the advertisement of cures.
8. Laws prohibiting the sale of remedies by drug stores and others without a prescription.

In addition to the above, great powers and wide discretion are granted to civil health authorities to deal with emergencies, it being understood, however, that all actions of civil health authorities are subject to judicial review.

It is recommended (1) that the Surgeon General of the U. S. Public Health

Service urge all state health authorities and through them the local health authorities in those localities where military and naval personnel may be assigned, to establish and maintain effective liaison with the appropriate Army and/or Navy medical officers for the purpose of fullest cooperation in venereal disease control, especially in case-finding activities, and to reduce to a minimum the number of exposures of military and naval personnel to infection with syphilis, gonorrhea and other venereal diseases; (2) that the Surgeon General of the Army and the Surgeon General of the Navy take similar action through appropriate channels to assure the active cooperation of Army and Navy medical officers for identical purposes; (3) that the Navy adopt a regulation requiring medical officers to report to appropriate civil health authorities all cases of infectious disease coming under their cognizance of which the civilian health authority would take cognizance were the same to occur in the community subject to its supervision; and to familiarize themselves with the public health laws and regulations of the communities in which they are located.

Dr. Moore read to the Subcommittee a preliminary report by the joint Committee on Prophylaxis of the American Social Hygiene Association and the U. S. Public Health Service, Dr. H. H. Hazen, Chairman, together with certain correspondence from Dr. Hazen and from Dr. Durrett of the U. S. Food and Drug Administration. It was agreed by the Subcommittee that the data furnished by Dr. Hazen's Committee and by Dr. Durrett were already adequately covered by the deliberations and previous recommendations of this Subcommittee.

Brief consideration was then given to the question of a revised diagnostic nomenclature for syphilis for adoption by Army and Navy, and it was agreed that Dr. Moore would prepare a more detailed memorandum on this point for circularization among members of the Subcommittee and its guests for consideration at the next meeting.

The Subcommittee then passed to a further consideration of certain of the administrative measures for venereal disease control in Army and Navy, and made the following specific Recommendation:-

It is recommended that in order to further the control of venereal diseases in the U. S. Army and Navy, all provisions relating to forfeiture of pay in the two Services in infected military and naval personnel, whether or not absent from duty and whether the disease was acquired at any time before or after entry into the Services, be forthwith repealed.

It is further recommended that naval regulations requiring mandatory Court martial in cases of venereal disease if "infection is discovered and reported by any other person than the man concerned", be amended to provide for Court martial discretionary with the commanding officer for attempted concealment of venereal infection.

It was further recommended that in order to avoid loss of man power and whether with present peace-time strength, the expanded conditions of mobilization for national defense, or actual war, venereally infected men should so far as possible be treated with their units. Where troop or naval concentrations permit, such patients should be centralized for diagnosis and treatment at ambulatory clinics, established ad hoc; or in connection with base, field, or mobile hospital units (e.g., in training camps, in cities, etc.). Where such large troop or naval concentrations do not exist, diagnosis and treatment should be the responsibility of unit medical officers. Special hospitals for venereally infected patients should not be created. Hospitalization should not be advised except in the case of actual disabling illness or resistance to ambulatory treatment methods. So-called infectious cases should not be hospitalized. Since infectiousness in syphilis and gonorrhoea is, for all practical purposes, immediately controlled by modern chemotherapeutic measures, provided that once started these measures are properly

continued, efforts to segregate infected men in hospital or in working quarantine should therefore be abandoned. Restriction of liberty and confinement to the limits of the station for two weeks after the start of treatment would seem to be the only necessary regulation.

There ensued some discussion as to the channels through which these particular recommendations should be submitted to U. S. Army and Navy, and the question was discussed, but not definitely decided, as to whether it might not be desirable to submit these regulations directly to the Chairman of the Military and Naval Affairs Committees, respectively, of the House of Representatives and of the United States Senate. Before arriving on a final decision on this point it was agreed that the various regulations dealing with punitive and administrative measures should be assembled by Dr. Moore and circularized further to all members of the Committee for consideration.

The Memoranda concerning gonorrhoea, chanoroid, lymphogranuloma venereum, and granuloma inguinale were formally adopted by the Committee as approved recommendations.

A Memorandum by Dr. Alyea on prophylaxis was also approved, and it was agreed by the Committee that the essential data from this Memorandum would be transferred to the history forms for gonorrhoea and for syphilis, now under process of revision by Doctors Stokes, Cox, and representatives of the International Business Machines Company.

The Subcommittee adjourned to meet early in September on the call of the Chairman.

MINUTES OF THE FIFTH MEETING OF THE SUBCOMMITTEE ON VENEREAL DISEASES
OF THE NATIONAL RESEARCH COUNCIL

JULY 12, 1940

The fifth meeting of the Subcommittee on Venereal Diseases of the Committee on Chemotherapeutics and Allied Subjects of the National Research Council, was held in Washington on July 12. Present were Dr. J. I. Moore, Chairman of the Committee; the following members of the Committee:- Dr. Ferrin Long, Dr. Oscar Cox, Dr. Edwin Alyea, Dr. Walter Clarke, Dr. John Mahoney, and Dr. John H. Stokes; and also the following guests:- Dr. Sanford Larkey of the Committee on Information of the National Research Council, Col. G. C. Hillman, Col. G. R. Callender, Col. J. C. Kimbrough, and Col. James Simmons, of the U. S. Army Medical Corps, and Capt. Charles Stephenson of the U. S. Navy Medical Corps.

Dr. Stokes presented a still further revision of the syphilis treatment sheet. It was agreed that Dr. Stokes would consult a representative of the International Business Machines Company, with the idea of still further condensation and rearrangement of this sheet for incorporation in Army and Navy Medical Records.

Dr. Larkey reported, in response to a question, that there was no objection to dissemination to Medical groups of the deliberations of this Committee, and that in fact arrangements were being made to publish in the Journal of the American Medical Association or elsewhere, certain of its conclusions when these are available.

The Committee and its guests then proceeded to consider the various memoranda submitted on the subject of gonorrhoea, lymphogranuloma venereum, granuloma inguinale, and chancroid. With still further revision, these memoranda were approved, and will be put in final form for mimeographing to distribution of all members of the Committee, and to the Executive Committee of the National Research Council.

These deliberations occupied almost the entire day.

At the end of the afternoon, there was again raised by Genr. Stephenson the issue of cooperation between Army and Navy Medical Corps and civilian public health authorities in the control of the venereal diseases. Dr. Walter Clarke was delegated to prepare a report, in which are supplied data as to civilian laws with reference to the reporting of venereal diseases, and the applicability of these laws to military and naval personnel; with recommendations to the U. S. Army and the U. S. Navy on the one hand; and on the other, to the U. S. Public Health Service and through the Public Health Service to State and local health officers, looking toward improved cooperative effort in the management of these diseases.

The Committee adjourned to reassemble on Friday, July 19, in Washington at 10 A. M.

MINUTES OF THE FOURTH MEETING OF THE SUBCOMMITTEE ON VENEREAL DISEASES
OF THE NATIONAL RESEARCH COUNCIL

JULY 5, 1940

On July 5, 1940, there was held at the National Research Council in Washington, D. C., the fourth meeting of the Subcommittee on Venereal Diseases. Present were Dr. J. E. Moore, Chairman; the following members of the Subcommittee:- Doctors John H. Stokes, Oscar Cox, Edwin Alysa, J. F. Mahoney, Walter Clarke, and (ex officio) Perrin Long; and the following guests:- Dr. Sanford Larkey of the Committee on Information of the National Research Council, Col. C. C. Hillman, Col. G. R. Callender, Col. James Simmons, and Col. James C. Kimbrough, all of the U. S. Army Medical Corps, Commander Charles Stephenson, U. S. Navy Medical Corps, and Dr. Robert H. Onstott, U. S. Public Health Service.

Col. Hillman reported, in regard to the Subcommittee's recommendation that junior medical officers be detailed for short courses of special training in venereal diseases, that the Army is now 900 medical officers short of complement for its already authorized increased personnel, and that at present such training seems impractical.

Dr. Larkey reported that the National Research Council has organized a Committee on Information, with Dr. Morris Fishbein as Chairman. The function of this Committee will be to correlate the activities of various Committees, and to arrange for the abstracting and publication of articles of military and naval importance in the Journal of the American Medical Association or elsewhere. Dr. Larkey, as a member of this Committee on Information, will have an office in Washington and will attend all meetings of all Committees.

Dr. Stokes brought up again the question of a new treatment sheet for syphilis, to be incorporated in Army and Navy medical records; and promised further revision of his original draft to provide space for late as well as for early

syphilis.

Dr. Cox opened the discussion on gonorrhoea. He submitted two Memoranda and a Resolution of the American Neisserian Medical Society, passed on June 11, 1940, which is quoted herewith:-

"RESOLVED, That the American Neisserian Medical Society notes and appreciates the appointment of Doctors Oscar F. Cox, Walter Clarke, John F. Mahoney, and Edwin P. Alyea to membership on the Subcommittee on Venereal Diseases of the Committee on Chemotherapeutic and Other Agents of the National Research Council, and that this Council be invited to make full use of the resources of the American Neisserian Medical Society."

Dr. Cox pointed out that in World War #1, the number of man-days lost from gonorrhoea was 4,000,000, and the number of discharges for disability 7000, both these figures being twice as great as the analagous figures for syphilis. The

management of gonorrhoea in the last War was atrocious.

Dr. Cox felt that the management of gonorrhoea was best carried out by (1) a small group of interested specialists; and next best, in order, by (2) general practitioners, (3) urologists, (4) syphilologists. He felt strongly that the general direction of the management of gonorrhoea in Army and Navy should be in the hands of the small group of physicians of group #1, and that they should cooperate in the provision of training facilities for a larger group of specialists and of junior medical officers. It was agreed that such cooperation in training is already provided for by a recommendation of this Subcommittee already passed, providing for general training in the venereal diseases.

Dr. Cox presented data from the Cooperative Clinical Group of the American Neisserian Medical Society and the U. S. Public Health Service (based on sulfanilamide results) to indicate that in acute gonorrhoea, a combination of local treatment and of sulfanilamide was superior to either method alone. Nevertheless, the Subcommittee agreed that newer results with sulfapyridine and probably also with sulfathiazole were so superior to those obtainable with sulfanilamide as to suggest that in Army and Navy the latter drug should be dropped in favor of the two former. As between sulfapyridine and sulfathiazole, it was further agreed that the choice lay with the former, because it has been so far more extensively studied, and because it is now readily available in quantity. Further, the Subcommittee agreed that in spite of Dr. Cox's evidence as to the value of local treatment in acute gonorrhoea, this form of treatment in inexperienced rather than expert hands was likely to do more harm than good, and should not be employed as a routine measure in Service practice.

Dr. Cox presented conclusive evidence as to the value of cultures in determination of cure in gonorrhoea. His data show that:-

If cure is determined on clinical grounds alone, one patient in 3

relapses.

If cure is determined by clinical status and smears, one in 20 relapses.

If cure is determined by clinical status and smears and culture, one in 100 relapses.

On the basis of these and other data as to the value of cultures, the Subcommittee adopted the following resolution:-

Resolved, that particularly for determination of cure in gonorrhoea, the laboratory services of Army and Navy Medical Corps should as soon as possible provide facilities for the cultural recognition of the gonococcus in body secretions.

There than ensued a general discussion of the Memoranda as to the diagnosis and treatment of gonorrhoea submitted by Doctors Cox and Alyea, in the course of which many suggestions for change were made. It was tacitly agreed that it would be the duty of the Chairman to incorporate these suggestions into a revised

Memorandum for submission in mimeographed form at the next meeting.

The Subcommittee specifically recommended that Army and Navy Medical Corps adopt, as promptly as possible for routine use in the management of patients with gonorrhoea, the admirable record form devised by the American Neisserian Medical Society and the U. S. Public Health Service, with such changes as might be necessitated by Service requirements. Dr. Cox was delegated to revise the form on this basis, and to present the revision at the next meeting.

The Subcommittee then considered the two Memoranda on lymphogranuloma venereum, submitted by Dr. Mahoney and Commander Stephenson. It was agreed that these Memoranda be amalgamated, with slight revision, by the Chairman, and submitted in mimeographed form at the next meeting.

Dr. Clarke reported that he had arranged in New York for immediate studies by five clinicians with ample clinical material on

1. Comparison of yolk-sac antigen with human pus antigen in diagnostic Frei test.
2. Studies of sulfathiazole in the treatment of acute lymphogranuloma.

The Subcommittee expressed its thanks to Dr. Clarke, and the hope that the results of these studies might be made available to it as soon as completed.

Dr. Moore read a letter from Dr. H. H. Hazen, Chairman of a Committee on Prophylaxis of the American Social Hygiene Association and the U. S. Public Health Service, offering the facilities of his Committee to the Subcommittee on Venereal Diseases. Dr. Moore had already replied to Dr. Hazen, gratefully accepting this offer, and asking that Dr. Hazen or a member of his Committee attend a meeting in the near future of this Subcommittee.

Dr. Adolf Rostenberg, Jr., of the U. S. Food and Drugs Administration, presented briefly to the Subcommittee certain of the problems of venereal disease prophylaxis, both chemical and mechanical. The Subcommittee felt itself unable to be helpful to Dr. Rostenberg's request for advice, except in minor respects. There was general interest, however, in the improvement of standards of manufacture and testing of condoms; and Dr. Rostenberg promised to furnish the Chairman with the present procedure of the Food and Drug Administration.

The Subcommittee adjourned to meet again in Washington on Friday,

June 12.

MINUTES OF THE THIRD MEETING OF THE SUBCOMMITTEE ON VENEREAL
DISEASE CONTROL OF THE NATIONAL RESEARCH COUNCIL

June 27, 1940

On June 27, 1940, there was held at the National Research Council, Washington, the third meeting of the Subcommittee on Venereal Disease Control of the Committee on Chemotherapeutics and Allied Subjects of the National Research Council. Present were Dr. J. E. Moore, Chairman of the Subcommittee, Dr. Lewis Weed; the following members of the Subcommittee: Dr. Perrin Long, Dr. Oscar Cox, Dr. Edwin Alyea, Dr. John F. Mahoney, Dr. Walter Clarke, Dr. John H. Stokes; and the following invited guests: Comdr. Charles Stephenson, U. S. Navy Medical Corps, Col. C. C. Hillman, Col. George R. Callender, Col. James S. Simmons, and Major L. L. Gardner, all of the U. S. Army Medical Corps, and Dr. N. B. Hon, Division of Venereal Diseases, U. S. Public Health Service.

The minutes of the preceding two meetings were approved without being read, since they had previously been circulated to all members of the Subcommittee.

Dr. Moore submitted for the consideration of the Subcommittee, a memorandum concerning the administrative control of the venereal diseases in Army and Navy, together with certain suggested recommendations. These memoranda are not herewith repeated, since they have been previously circulated to all members of the Subcommittee and its guests.

Items, I, II, and III of the Memorandum, dealing with education, physical inspection, and prophylaxis were generally discussed by the Committee and its guests. It was pointed out by the Army and Navy Medical Officers present that Army and Navy procedure in these respects is more identical than appears from the general orders and circular letters mentioned in the first paragraph of the Memorandum. For various admin-

istrative reasons, the Navy particularly prefers to deal with these matters by regulations issued through the Office of the Surgeon General than by general orders, and through these regulations and through long established custom, Navy and Army procedure are in effect identical.

In connection with the tentative recommendation that there be prepared for distribution to all officers and men of both Services, now engaged or to be enrolled, a booklet analogous to that distributed in World War #1, "Venereal Diseases. Facts Every Soldier and Sailor should know", it was brought out that for two years, Army has had such a booklet in preparation which is now undergoing scrutiny by the General Staff; but permission to print and distribute this booklet is expected in the near future.

It was pointed out by Comdr. Stephenson that if this recommendation were adopted by the Committee, the preparation of such a booklet by the Navy Medical Corps would be a matter of extreme difficulty, for various administrative reasons, and that it would probably be desirable to have such a booklet prepared by and distributed by an outside civilian organization, such as the American Social Hygiene Association.

For the improvement of the administrative control of the venereal diseases, the following recommendation was unanimously adopted by the Committee:

It is recommended that each Service should immediately create within the offices of their respective Surgeons General, a Section of Venereal Disease Control, distinct from and equivalent to the Section of Infectious or Communicable Diseases, to be headed by a properly senior officer who shall if possible have had training in public health.

Recommendation

This officer should be furnished with appropriate professional and clerical aid. This section should be charged with sole responsibility for prevention, diagnosis, and treatment of the venereal diseases within the respective Services.

It was further recognized by the Subcommittee that Medical Officers of both Services should receive constant further instruction in the presentation, diagnosis and treatment of the venereal diseases. To this end the following recommendations were unanimously adopted by the Subcommittee:

Recommendation

Each Service should immediately provide a group of officers, specially trained in the venereal diseases, in the proportion of at least one such officer to every 50,000 strength. If such officers are not already available, they should be detailed for special training in all types of venereal disease for minimum periods of six months, at selected civilian university training centers. These officers should act as instructors and consultants, peripatetic if necessary, to junior Medical Officers.

Recommendation

It was further recommended that junior Medical Officers with units, charged with actual supervision of prophylaxis and diagnosis and treatment of venereal diseases, should receive special instruction as necessary from the consultant officers mentioned in the previous recommendation. Until such instruction is available, short training courses for such officers should be at once provided in civilian university instruction centers. It is further recommended that such junior Medical Officers be detailed for this type of instruction by the Army and Navy Medical Corps.

Recommendation

It was further recommended that for the benefit of all Medical Officers of both Services, there should be promptly prepared for general distribution among them, a booklet, providing in succinct summary form, all prophylactic, diagnostic and treatment procedures to be used in the venereal diseases.

In connection with these several recommendations, it was pointed out that the Navy Medical Corps already possesses a Section of Venereal Disease Control, while the Army Medical Corps does not. Furthermore, the Navy already possesses a number of officers specially trained in the venereal diseases, who are already competent to act as consultants. The Army, however, does not, and should make immediate arrangements for the training of such Officers.

It was further pointed out that short courses in venereal diseases for junior Medical Officers could be speedily organized in various portions of the country, notably in Philadelphia, New York, Boston, Nashville, St. Louis, Hot Springs, Arkansas, and San Francisco. Longer training courses for the instruction of consultants are already available in Baltimore and perhaps elsewhere.

It was further pointed out, with reference to the proposed booklet, that such a booklet is already in the process of preparation by the Committee on Chemotherapeutics and Allied Subjects, in which the venereal diseases may be readily incorporated.

Items IV and V of the Memorandum, dealing with forfeiture of pay and disciplinary action, were not discussed, having been held over for discussion at the next meeting. The same applies to Items VII and VIII, dealing with segregation and treatment, and notification to

health officers of personnel discharged from the Services with venereal diseases, which were discussed only incidentally and should be further considered at the next meeting.

At the request of Col. Hillman and owing to the presence of Major Gardner, the Committee proceeded to discuss Item VI of the Memorandum, dealing with reports and records. This discussion led into a consideration of the succinct and comprehensive outline submitted by Dr. Stokes for the management of syphilis in the Army and Navy under emergency conditions. This outline was discussed in detail by the Subcommittee and its guests, and with minor changes, was recommended for adoption by Army and Navy Medical Corps. The outline is being mimeographed and will be submitted to all members of the Subcommittee and its guests within the next few days.

Comdr. Stephenson brought up for consideration, the U. S. Navy Medical Corps data on arsenical reactions. The Subcommittee unanimously agreed that these data are the most complete existing anywhere in the medical literature, and specifically recommended that the Navy Medical Corps continue to collect and analyze such data, which are of benefit, not only to the Navy, but to the Medical profession as a whole.

Dr. Moore read to the Committee certain correspondence from Dr. R. A. Vonderlehr and Dr. Harry Eagle, concerning the adoption of the Eagle flocculation test by Army and Navy Medical Corps, and agreed to send copies of this correspondence to Col. Hillman, Col. Callender and Comdr. Stephenson.

Dr. Moore also read to the Committee a letter from Dr. Adolph Rostenberg, Jr., of the U. S. Food and Drug Administration, requesting a conference on venereal disease prophylactics. It was agreed that

Dr. Rostenberg be asked to attend the next meeting of the Committee on Friday, July 5 at 3.30 p.m.; and to present his discussion to the Committee as a whole.

For consideration of the Committee at the next meeting on July 5, there remain the following items:

1) Certain portions of the memorandum dealing with administrative procedures.

2) Suggested modification and standardization of diagnostic terms for syphilis in Army and Navy.

3) Memorandum submitted by Dr. Cox on the treatment of gonococcal infection.

4) Memorandum submitted by Comdr. Stephenson on lymphogranuloma venereum.

At 4:45 P. M. the Committee adjourned.

MINUTES OF THE SECOND MEETING OF THE SUBCOMMITTEE ON VENEREAL DISEASE

CONTROL OF THE NATIONAL RESEARCH COUNCIL

June 13, 1940

On June 13, 1940, there was held at the Hotel Roosevelt in New York the second meeting of the Subcommittee on Venereal Disease Control of the Committee on Chemotherapeutics and Allied Subjects of the National Research Council. Present were Dr. J. E. Moore, Chairman of the Subcommittee, Dr. Ferrin Long, Dr. Oscar Cox, Dr. Edwin Alyea, Dr. John F. Mahoney, Dr. Walter Clarke, Dr. John H. Stokes, members of the Subcommittee, and the following invited guests: Comdr. Charles Stephenson, U. S. Navy Medical Corps, Capt. Douglas Kendrick, U. S. Army Medical Corps, Dr. C. C. Pierce, U. S. Public Health Service.

The first portion of the meeting was devoted to the reading of the Minutes of the first meeting of June 7. Numerous corrections and additions to these first Minutes were suggested which have now been incorporated into the Minutes of the first meeting and will be enumerated but not repeated in these Minutes. These corrections and additions are as follows:-

In paragraph I-C of the Minutes of the first meeting is an addition concerning experimental work on the physiologic effects of the sulfonamid compounds.

In paragraph II of the first Minutes is an addition representing an approved recommendation for liaison of the Medical Corps of the Army and Navy with civilian health authorities.

Paragraph V-A dealing with diagnostic procedures in gonorrhoea has been largely rewritten.

The paragraphs under V-B dealing with the diagnosis of syphilis have also been largely rewritten.

The remainder of the second meeting was devoted to further consideration of the general management of and diagnostic procedures in the several venereal diseases, to be standardized so far as possible for use in the armed forces.

In this connection it was agreed that Comdr. Stephenson and Capt. Kendrick would forward immediately to Dr. Moore, as chairman of the Subcommittee, multiple copies of all existing regulations concerning venereal disease in the U. S. Army and Navy; that Dr. Moore would summarize these regulations, together with others which may have been in effect during the World War No. I, and would circularize the Subcommittee and its guests within a few days with a summary and recommendations for general administrative procedure in the control of the venereal diseases.

It was further agreed that Dr. Stokes would prepare and circularize among the Subcommittee and its guests an outline of treatment for syphilis applicable to the armed forces, and that in this connection Comdr. Stephenson and Capt. Kendrick

would forward immediately to Dr. Stokes multiple copies of the record forms now in use in Army and Navy.

It was further agreed that the diagnosis files for venereal disease for the Army and Navy should be standardized and identical; and that Comdr. Stephenson and Capt. Kendrick would forward at once to Dr. Moore copies of the diagnosis files now in use with a view to securing uniformity.

It was further agreed that Dr. Oscar Cox would adapt for the Sub-committee the recommendations of the American Neisserian Medical Society for the treatment of gonorrhoea.

Dr. Mahoney was instructed to prepare memoranda concerning the diagnosis and treatment of lymphopathia venereum and of chaneroid, and to circularize these among the Subcommittee members and its guests. In this connection Dr. Moore promised to send to Dr. Mahoney immediately a recent unpublished paper by Dr. Ira Schamberg on the treatment of lymphopathia venereum with sulfanilamide.

Comdr. Stephenson was instructed to prepare for the Committee a memorandum on granuloma inguinale.

It was the consensus that these various memoranda should be prepared as promptly as possible, mimeographed, and circularized to all members of the Subcommittee and its guests, if possible, prior to the next meeting of the Subcommittee on Thursday, June 27th, in Washington.

At this point the Committee adjourned.

MINUTES OF THE MEETING OF THE SUBCOMMITTEE ON VENEREAL DISEASE
CONTROL OF THE NATIONAL RESEARCH COUNCIL

June 7, 1940

On June 7, 1940, there was held at the National Research Council in Washington, D.C. an organization meeting of the Subcommittee on Venereal Disease Control of the Committee on Chemotherapeutics and Allied Subjects. Present were Dr. Lewis Weed, Chairman of the Division of Medical Sciences, National Research Council; Dr. Ferrin Long, Chairman of the Committee on Chemotherapeutics and Allied Subjects; Dr. J. E. Moore, Chairman of the Subcommittee on Venereal Disease Control; Dr. Oscar Cox, Dr. Edwin Alyea, Dr. John F. Mahoney, Dr. Walter Clarke, and Dr. John H. Stokes, members of the Subcommittee on Venereal Disease Control; and the following invited guests: Commander Charles Stephenson, U. S. Navy Medical Corps, Col. C. C. Hillman, Col. George R. Callender, and Col. James S. Simmons, all of the U. S. Army Medical Corps; and Dr. R. A. Vonderlehr, Assistant Surgeon General, Division of Venereal Diseases, U. S. Public Health Service.

The meeting was opened by Dr. Weed who described briefly the formation of these various committees of the National Research Council, at the suggestion of the Surgeons General of the U. S. Army and Navy. The purpose of the committees as described by Dr. Weed is to offer informally to the Army and Navy Medical Corps suggestions dealing with problems which may confront the two services in the event of a national emergency. Following this description by Dr. Weed, the meeting was turned over to the chairman, Dr. Moore.

At the request of Dr. Moore, Colonel Hillman and Commander Stephenson briefly described the problems relating to venereal disease which confront the Army and Navy at present and in the face of the possibility of a national emergency. Dr. Vonderlehr described the arrangements of the Public Health Service for cooperation with the armed forces in connection with the control of venereal disease in the civilian population, particularly in areas contiguous to troop or naval concentrations.

As a result of the general preliminary discussion, in the course of which numerous questions were asked of representatives of the Army, Navy and Public

Health Service by members of the Committee, a tentative agenda for consideration by the Committee was drawn up to cover the following ten points:-

- I - Prophylaxis of the venereal diseases - chemical, mechanical, and chemotherapeutic.
- II - Liaison of the Medical Corps of the Army and Navy with the U. S. Public Health Service and with voluntary organization of civilian agencies for the control of venereal disease. Under this heading are such items as (a) the epidemiologic approach to venereal

disease control by means of contact tracing in the armed forces; (b) substitutive methods of control in the armed forces; (c) the control of venereal diseases in the civilian population, particularly in areas contiguous to the armed forces; by public health, medical, and legal measures.

III - The desirable features of examination of enlisted men of the Army and Navy at their induction into the services.

IV - Methods of case finding in the armed forces after enrollment, including particularly periodic inspection of troops.

V - Diagnostic procedures as to the several venereal diseases, to be standardized so far as possible for use in the armed forces.

VI - Treatment procedures for the several venereal diseases in the armed forces considering the special problems which may confront each of them under varying conditions of service and mobilization.

VII - Legal measures for control of the venereal diseases in the Army and Navy.

VIII - The management of venereally infected personnel at the time of demobilization.

IX - Research investigations, particularly required by the Army and Navy.

X - Personnel especially trained in venereal disease control to be enrolled in the two services in the event of a national emergency.

The first six items on these agenda received some discussion by the Committee with the assistance of its guests, and the following general conclusions were reached:-

I - Prophylaxis. The Committee recommends, in order to reduce the incidence of the venereal diseases in the armed forces -

A) An intensification of educational effort with enlisted and officer personnel;

B) The continued utilization of all known chemical and mechanical prophylactic methods.

Under this heading the methods of chemical prophylaxis now in vogue in Army and Navy were described. The prevailing system of chemical prophylaxis is that generally in use since the last war and including the establishment of prophylactic stations where possible, under the direction of trained hospital corps personnel; thorough washing with soap and water; the intra-urethral injection of a silver salt; and the local application of 33 per cent calomel ointment. In the Navy in small units where the setting up of prophylactic stations is not feasible, tube prophylaxis is used. There are no satisfactory data as to the relative value

of tube and station prophylaxis.

As to mechanical prophylaxis, condoms are readily available both to Army and Navy personnel though their distribution might perhaps profitably be extended. It was the general feeling of the Committee that both at present and in the event of mobilization, the use of mechanical prophylaxis by the armed forces should be made even more readily available than at present.

C) The Subcommittee further recommended that research is desirable both in the fields of chemical and therapeutic prophylaxis, as to the possibilities of newer compounds in the control of gonorrhea and syphilis.

In this connection was brought up the possible prophylactic use of sulfonamid compounds in the control of gonorrhea. The question was raised as to the physiologic effects of such small doses of these compounds, particularly sulfapyridine and sulfathiazole, as would probably be necessary for prophylaxis with respect to their influence on muscular coordination in such highly specialized occupations as aviation, gun-pointing, etc. To the Committee's knowledge physiologic data of this nature are lacking. It was thought possible that the Civil Aeronautics Authority might have conducted experimentation in this direction; and Commander Stephenson of the Navy promised to communicate with the Civil Aeronautics Authority to determine if such experimentation had been done and with what results. He will report his findings at the next meeting of this Subcommittee.

It was felt by the Committee that if experimentation of this nature has not already been conducted by the Civil Aeronautics Authority or by the Departments of Aviation Medicine of the Army or Navy Medical Corps, a request for such experimentation might properly be made by this Subcommittee to one of these agencies. The desirability of physiologic knowledge in this respect applies not only to the possible use of sulfonamid compounds in the prophylaxis of the venereal diseases, but also to their use in the treatment of actual cases of gonorrhea.

A subsequent report (at the second meeting of the Committee) of Commander Stephenson is to the effect that no experimental work of this nature has been performed. It was then decided that Commander Stephenson and Captain Kendrick would

confer with their respective Chiefs as to the feasibility of carrying out such studies within the Army or Navy Medical Corps.

It was further felt by the Committee that clinical experiments with the sulfonamid compounds in the prophylaxis of gonorrhoea should be carried out by the Army or Navy, or both; and that since this experimentation seems impossible on an obligatory basis, it would be desirable at the earliest possible moment for certain selected units to attempt it on a voluntary basis.

The chemotherapeutic prophylaxis of syphilis was also discussed.

particularly in connection with the possible use of oral sobisminol. Further animal experiments carried out by Hanzlik have indicated that this preparation may be of value in the prophylaxis of syphilis in the rabbit. These experiments should perhaps be repeated. It was agreed that a copy of Hanzlik's paper, as yet unpublished, would be sent as soon as possible to Dr. Mahoney who would report later on the desirability of further experimental or possible voluntary clinical use of sobisminol in the prophylaxis of syphilis.

II. Liaison of the Medical Corps of the Army and Navy with the U.S. Public Health Service and with voluntary organization of civilian agencies for the control of venereal disease.

Dr. Vonderlehr presented to the meeting a memorandum drawn up by the U. S. Public Health Service outlining certain policies of agreement between the Public Health Service and the Medical Corps of Army and Navy. This memorandum was referred by the Subcommittee to Dr. Walter Clarke with instructions to present at the next meeting a revision of it for consideration.

At the second committee meeting on June 13, Dr. Clarke submitted the following, which was approved as the Committee's recommendation:-

The development of adequate facilities and services in civilian communities for the diagnosis, treatment, and public health control (including the isolation of infectious cases when indicated) of syphilis and gonorrhea contributes to the protection from infection of military, naval, and essential industrial personnel in the vicinity of such communities. The Army and Navy should cooperate with appropriate civilian health authorities in facilitating contact examinations and other epidemiologic activities intended to control the spread of infection. Since it is desirable to reduce to a minimum opportunities for exposure to venereal infections, the Army and Navy should join with the United States Public Health Service in supporting vigorous enforcement of state laws and city ordinances against prostitution, and should recognize the cooperation and efforts of accepted voluntary agencies to rally and organize public support to this same end.

III. The desirable features of examination of enlisted men of the

Army and Navy at their induction into these services.

Representatives of the Army and Navy described the present method of examination of enlisted and officer personnel at entry into the armed forces. An examination for gonorrhoea is part of the routine physical examination. Both in Army and Navy at present a routine serologic test is done at enrollment. In the Navy an enrollee with a confirmed positive serologic test is rejected without prejudice and this will continue to be the policy even in the event of mobilization. In the Army an enrollee with a positive serologic test is accepted and will be so

accepted in the event of mobilization.

The Subcommittee recommends so far as syphilis is concerned that, in the event of a national emergency:-

a) The use of a routine serologic test on all men inducted into the Services be continued, with the aid of State and local health department laboratories if necessary.

b) In all enrollees, including those with negative serologic tests, a history of preceding syphilitic infection and possible treatment therefor be routinely enquired for; and

c) Every effort be made to reject completely prospective personnel with obvious clinical evidence of neurosyphilis or cardiovascular syphilis. For the detection of the former, and since complete and expert neurologic examination is not likely to be available from all draft boards, there should be required as a minimum an examination of the pupillary reactions of all candidates for enrollment. Those with pupillary abnormalities suggesting the presence of neurosyphilis should be further examined with this diagnosis in mind and, if the diagnosis is confirmed, such candidates should be rejected.

It was the feeling of the Subcommittee that the information concerning syphilis to be obtained by the proposals outlined above at the time of induction into the Services will prove to be of great importance, not only as to the medical management of syphilitics discovered at the time of this examination and the branch of the Services in which, respectively, they might be enrolled, but also with reference to subsequent claims for compensation after demobilization.

IV. Methods of case finding in the armed forces after enrollment,
including particularly periodic inspection of troops.

In both Army and Navy present practice continues as previously that in prophylactic stations an examination for obvious signs of venereal disease is made by Hospital Corps attendants when prophylaxis is applied for. This practice should continue.

Periodic inspection for venereal disease of all enlisted personnel continues to be carried out in both Army and Navy at approximately monthly intervals by means of surprise examinations. These inspections are, however, less valuable than formerly since the punishment regulations for the acquisition of venereal disease, to be discussed under Item VII below, have been relaxed. Nevertheless, it was the feeling of the Subcommittee and of its technical advisers, that inspection for venereal disease should continue to be a part of the monthly physical inspection of all enlisted personnel.

V. Diagnostic procedures.

A. As to gonorrhoea, the Subcommittee recommends that any purulent urethral discharge should be regarded as gonorrhoea and laboratory confirmation of this diagnosis should be immediately sought. Treatment for gonorrhoea should not be instituted until laboratory confirmation is obtained, provided the laboratory examination can be obtained within 24 hours. If laboratory facilities are not so immediately available, treatment by appropriate chemotherapeutic measures may be instituted at once. However, the Subcommittee further recommends that the diagnosis of gonorrhoea should not become a part of the Service record of the enlisted man or officer in question unless and until supported by laboratory evidence.

It is further recommended that in order to promote case finding of symptomless syphilitic infection, a follow up serologic test for syphilis should if possible be performed in all cases with a diagnosis of gonorrhoea 4 to 6 months after the putative gonorrhoeal infection was acquired.

P. As to the diagnosis of syphilis, the Subcommittee recommends that in the augmented forces of the Army and Navy which may be caused by a national emergency, the diagnosis of syphilis continue to be, as it is at present, a laboratory procedure involving the use of darkfield examination, serologic tests, or both.

The Subcommittee further recommends that when the diagnosis of syphilis has been established by such laboratory procedures in any onlisted man or officer, as soon as may be practicable thereafter, the patient shall be examined by a designated specially trained medical officer in order to define the type of syphilitic infection and to outline appropriate treatment.

From the laboratory standpoint it is recommended that for routine diagnostic purposes (also to be used as a routine test on all troops at the time of enrollment in the event of mobilization and later demobilization) there shall be adopted for the armed forces the Eagle flocculation test. If the initial Eagle test is negative, it need not be repeated unless clinical evidence justifies it. If the initial test is positive or doubtful, it should be repeated to rule out technical error before the diagnosis of syphilis can be considered to be established. If the second Eagle test is positive or doubtful, this should be verified where the

military or naval exigencies of the situation permit, by a Kolmer complement fixation technique. The Kolmer anti-sheep system should be adopted in place of the anti-human system now in use in the United States Army. It is recognized that this recommendation involves an alteration in procedure in the existing serologic laboratories of both Army and Navy, but it is felt that the necessary changes in technique should be instituted immediately and as rapidly as possible.

It is further recommended that all antigens for serodiagnostic tests for S yphilis sold in interstate commerce be brought under the supervision of the ^{Biologic}ologic Control Act.

END

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