

AVIATION MEDICINE SPECIAL (CAM) REPORTS  
VENEREAL DISEASES, CONFERENCES

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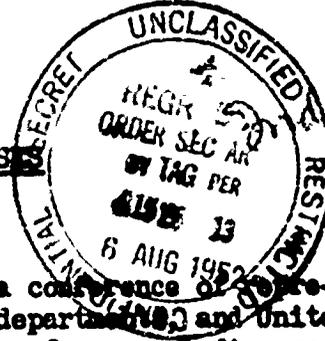
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NATIONAL RESEARCH COUNCIL

Memorandum on  
BRITISH JOINT COMMITTEE ON VENEREAL DISEASES

October 13, 1943.



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In April 1943 there was held at the Home Office a conference of representatives of the Home Office, other interested Government departments, and United States and Canadian Army authorities to discuss the problems of venereal disease with special reference to the situation as affecting American and Canadian Forces in Britain. This conference recommended the appointment of a committee of experts "to consider what further action could be taken within the framework of the existing legislation and ... what amendments of the law, if any, were desirable and practicable."

The Committee was appointed in June 1943 under the Chairmanship of Sir Walter Dalrymple-Champneys, Bart. D.M., F.R.C.P. Ministry of Health. It included originally representatives of the War Office, Air Ministry, Canadian Army, United States Army, Ministry of Health, Home Office, Metropolitan Police, Department of Health for Scotland, and Scottish Home Department. Subsequently there has been added a representative of the Admiralty.

The Committee has held eight meetings from June 25 to September 24, 1943.

The Committee has been to make recommendations to appropriate British Government Ministers and agencies regarding an amplified program for the control of venereal disease in the civilian population. Its deliberations have covered four major issues: first, education; second, case-finding; third, improved methods of treatment; and fourth, control of prostitution. The Committee had felt themselves free to consider and make recommendations on any suggested further steps which appeared desirable and practicable to reinforce present measures to control the growing incidence of venereal disease. The four purposes enumerated above are considered from the standpoints of (a) what is already being done; (b) what expansion or improvements seem possible under the existing legislation and present state of public opinion; and (c) what further action, possibly by means of new legislation, appears desirable.

The first eight meetings have been devoted largely to the problems of education and case-finding.

On September 29, 1943, the Committee has issued an Interim Report on these two topics, and has recommended:

- I. That the B.B.C. be approached through the Ministry of Information as to the possibilities of providing increased facilities for the presentation of the subject of venereal diseases in their broadcast programs, preferably in the late evening hours.
- II. That effort be made to persuade the Press to devote more space to the subject of venereal disease through the medium of editorials and news articles in addition to continuing the present paid advertisement campaign.

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III. That the Board of Education, the Scottish Education Department, and the Organizations responsible for the junior services, such as the G.T.C., W.J.A.C., A.T.C., Sea Cadets and Junior Training Corps, be asked to encourage the initiation or development of sex education, including the subject of venereal disease by such means as seem appropriate.

IV. That the British Dominions and Allied Services be urged to continue and extend educational work on the subject of venereal diseases amongst the men and women serving in their respective Forces.

V. That the Ministry of Labour and National Service be asked to facilitate propaganda on the subject of venereal diseases in factories, hostels, and amongst other aggregations of work-people; also in hostels and groups supervised by Seamen's Welfare Committees.

VI. That efforts be made to secure more intensive action by the responsible local authorities in the local spread of education on the subject of venereal disease aimed at reaching the individual, and that local authorities be urged to provide personnel qualified to impart such education and to give special attention to the importance of small group education, e.g., the inauguration of talks, and discussions, for small groups of parents, teachers, and leaders of public opinion.

VII. That action under recommendation (VI) be followed up after an appropriate interval by visits from selected officers from the Ministry of Health, or other central body, to ascertain the extent of the local authorities' efforts and to exercise persuasion and give advice where it appears desirable; such visits to be concentrated on those localities in which the evidence suggests that members of the British and Allied Forces most frequently contract venereal disease.

VIII. That as part of general medical education organized instruction relating not merely to diagnosis and treatment, but to the preventive aspect of venereal disease be given to medical students; that lectures and addresses on this aspect be also given to local medical societies; and that the Deans of medical schools of the British Medical Association be approached with this object.

\* \* \* \* \*

As to case-finding, the Committee "have noted with interest the degree of success attained by the arrangements which the American Army Authorities are operating in certain areas in this country, including London, in cooperation with the local health authorities under which selected nurses of the United States Army, known as public health nurses, seek out contacts who have been named by members of their Forces, and by tactful and discreet approach endeavor to gain the confidence of the contact and secure examination and, if necessary, treatment."

In view of these and other considerations the Committee has recommended:-

IX. That Medical Officers of Health of venereal diseases Authorities "should develop to the fullest possible extent the tracing and following-up of contacts ascertained through information given by patients, or otherwise, in order to secure the early examination and, if necessary, continuous treatment of contacts, and to stop the spread of infection."

X. That the work of contact tracing and following-up should be regarded as a definite part of the function of the Treatment Center.

XI. That while the choice of personnel employed in the work of contact tracing and following-up must rest with the local Authority, so far as is practicable persons with a background of training in nursing and public health work, and the experience of home visiting should be employed for contact-tracing, and persons with training and experience in almoner-social welfare work for facilitating attendance and follow-up work."

XII. That every effort should be made to develop this work in spite of the restrictions or the current availability of suitably trained personnel, particularly by those local Authorities in whose areas there is evidence of a high incidence of venereal disease.

XIII. That the visits by selected officers to areas of high incidence of venereal disease, suggested by the Committee in their recommendation (VII) above, should include such enquiries and advice as appear desirable in relation to contact-tracing and follow-up work.

The Committee has considered the relationship of Regulation 33-B to the preceding recommendations on contact-tracing, and the unwillingness of many Medical Officers of Health to undertake informal action outside the protection of the Regulation for fear of legal proceedings, and have recommended:

XIV. That Medical Officers of Health be encouraged to take all practicable steps to secure the effective tracing of contacts (and the following-up of patients under treatment) from information received on Form 1 (Regulation 33-B) or through other channels; and that appropriate action be taken to overcome as far as possible the doubts of many Medical Officers of Health as to their legal position in undertaking these duties whether personally or through the medium of other Officers to whom such duties may be delegated.

The Committee has also considered the desirability of further extension of routine serologic testing in case-finding, and has recommended:

XV. That the importance of making the fullest use of laboratory procedures be impressed upon medical practitioners as a part of the educational program, stress being laid at the same time on the difficulties in technique and interpretation, and the need for regarding a positive result in such tests only as indicating the need for further investigation; that extensions of laboratory facilities

be provided wherever required, and that such facilities be of the highest possible standard.

XVI. That efforts be made to secure the adoption of the principle of routine blood testing for syphilis in the case of every pregnant woman; that Welfare Authorities, in particular, be urged to make the fullest use for this purpose of the laboratory facilities at present available; and that the expansion of laboratory facilities to provide for this and the other laboratory tests recognized as being necessary, be actively encouraged.

The United States representative on the Joint Committee on Venereal Diseases is Colonel John E. Gordon, Division of Preventive Medicine, United States Army, and the Canadian representative Lieut. Colonel M. H. Brown, who occupies the same position in the R.C.A.M.C. There is reason to believe that Colonel Gordon and Colonel Brown have exercised a powerful influence in the deliberations of the Joint Committee.

A letter of October 4, 1943, from Colonel Gordon says:

"Our deliberations about the third principal interest, that of repression of prostitution, are well under way and, while decision has not yet been taken, what has been agreed upon tentatively is more far reaching and purposeful than I had reason to believe might be accomplished at this time."

These recommendations of the Joint Committee on Venereal Diseases considered concurrently with a memorandum submitted by J. E. Moore to the National Research Council on Venereal Disease Control in Great Britain, indicate that the British authorities have taken a series of far reaching steps in venereal disease control in that country. These steps have been prompted, not only by the substantial increase in venereal disease in the British civilian population, which has occurred since 1940, but also by the importance of this increase and of the relatively high rates in the Canadian and American Armies in respect of Anglo-Canadian and Anglo-American relations.

This summary of the proceedings of the Joint Committee is circularized at this time to suggest that the British authorities are doing their best to meet the problems which have arisen as a result of the War, and that Anglo-American relations will be fostered by continued and extended active cooperation on the part of the United States Army, United States Navy, and United States Public Health Service (in respect of the Merchant Marine).

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

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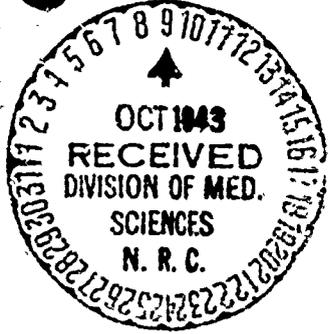
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MINUTES OF A CONFERENCE  
On Chemical Prophylaxis of Venereal Disease

Held under the auspices of the Subcommittee on Venereal Diseases

September 20, 1943



Present at the Conference with the following persons:

- From the United States Army - Col. S. M. Corbett, Lt. Col. T. B. Turner, Lt. Col. R. W. Prentiss, Maj. E. Wambach, Maj. Robert Dyar, Capt. G.D. Larimore.
- From the United States Navy - Comdr. W. H. Schwartz, Comdr. A. J. Percyra.
- From the Subcommittee on Venereal Diseases - Drs. J. E. Moore and J. F. Mahoney.
- From the U.S. Public Health Service - Dr. Harry Eagle.
- From the HEC-OM - Drs. Lewis Weed, T. B. Forbes, and C.K. Anderson.
- From the Food and Drug Administration - Dr. Herbert O. Calvery, Mr. Geoffrey Woodard, and Mr. E. P. Lang.
- From the Warner Institute for Therapeutic Research - Dr. M. R. Thompson.

This Conference was called on the basis of the following letter from Lt. Col. Roger Prentiss, Jr. to Dr. Lewis Weed:

9 September 1943

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

Dear Doctor Weed:

The Surgeon General has directed me to present for your consideration the subject of individual venereal disease prophylactic packets. There has been demonstrated a very definite need for individual packets to supplement station prophylaxis in the Army. One such packet has been issued in considerable amounts but has not been entirely satisfactory. It is rather complicated to use and defects have appeared in the tube containing silver picrate.

It would appear to be desirable to adopt as soon as practicable a one-tube ointment which would be effective against venereal disease. Considerable work along this line has been carried on by civilian investigators. It is believed to be desirable to obtain an early comprehensive review of their work so that there may be an early initiation of any necessary further studies of materials for individual prophylactic packets.

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It is requested that this subject be referred to an appropriate committee or a conference group of your organization and that this office be favored with your comments and recommendations. It seems probable that discussion may develop the fact that further studies of prophylactic ointments will be necessary before any one can be recommended for adoption. If such proves to be the case it is anticipated that no difficulty will be encountered in arranging for trials at one or more military stations.

Sincerely yours,

S/ ROGER G. PRENTISS, JR.  
Lieut. Colonel, Medical Corps,  
Assistant.

After a brief preliminary discussion the Chairman summarized the available information on chemical prophylaxis which has grown out of the series of investigations carried out on various OSRD contracts under the auspices of the Subcommittee on Venereal Diseases.

SYPHILIS. It has been shown (Eagle) that 33 per cent calomel ointment probably has some protective effect in experimental animals in the approximate dose administered to man, e.g., 25 mg/kg, and has a definite protective effect at 50 mg/kg. It has been further shown (Fleming) that the protective effect of calomel ointment depends, at least in part, on particle size, and that micronized ointments, whether particles of 5 micra or less, are more effective than those of larger particle size. The effect of bases has been studied (Chesney) and it was found that 33 per cent calomel in a vanishing cream base was ineffective. These experiments, however, are not exactly comparable to the experiments of Eagle and Fleming since the time intervals between inoculation and treatment differed and particle size was not controlled.

The effect of calomel has been shown to be both local and systemic (Eagle and Mahoney). The mechanism of its action is not clear.

The absorption of irritating properties of calomel (and sulfonamides) have been studied (Calvery and Thompson). Absorption of both compounds is better from a water soluble vanishing cream base than from the Army petrolatum lanolin base.

It has been shown (Eagle) that a number of arsenical drugs falling into the general groups of the amide substituted phenylarsenoxides are effective in the prevention of syphilis in experimental animals. In these experiments the inoculations were made into a cut carried almost through the depth of the skin and rubbed with a suspension of approximately 10 million organisms per cubic centimeter. The arsenicals have been applied in a propylene glycol solution. 0.5 c.c. of a 0.2 - 0.4 per cent solution protects if applied within four hours after inoculation, and stronger concentrations will protect up to 22 hours. The results are local and not systemic, since 50 times the concentration which is protective when applied locally does not protect when applied on the opposite side of the back. The arsenicals are effective also as pre-prophylaxis. An inoculation made into a skin area at which the arsenicals have been previously applied, remains ineffective. The prophylactic ef-

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ficacy of arsenical drugs is apparently directly related to their in vitro treponemocidal activity. Preliminary results, utilizing the arsenicals in an ointment base instead of propylene glycol solution, indicate (Eagle) that they are also effective and that there is no loss of spirocheticidal activity. The choice of an arsenical drug for prophylaxis will depend, considering the essentially similar prophylactic activity of about twenty different compounds, on the local toxicity and ease of manufacture of these preparations.

The IRRITATING EFFECT OF THE ARSENICALS. This has been studied for a number of compounds (Galvey); tested on rabbit skin, the mucous membrane of the rabbit penis, the rabbit conjunctiva, and human skin by patch tests. Certain compounds are more irritating than others and 7 of those listed are apparently too highly irritating to be of use in human beings. Two of those which are most effective in vitro and in prophylactic experiments (4-COME<sub>2</sub> - phenylarsenoxide and 4-NEOME<sub>2</sub> - phenylarsenoxide) are in concentrations as high as 0.4 per cent only slightly irritating to a degree comparable to that observed with the present Army prophylactic calomel ointment. The degree of irritation can be still further modified by a change in base.

CHANCROID. Various prophylactic agents have been studied in various inoculations of human beings (Combes, Greenblatt). The observers agree that

- (a) soap and water is ineffectual
- (b) calomel ointment is ineffectual
- (c) sulfonamide ointments are effectual in concentrations varying from 5 - 20 per cent. Sulfathiazole was the more effective of those tested. The variation in concentration appears to effect prophylactic results only slightly and a 10 per cent ointment is probably as effective as a 20 per cent.
- (d) All of the arsenic preparations so far tried are ineffectual.
- (e) Of various wetting agents employed, saphiran is effectual in 0.5 per cent concentration, but is too irritating for use.

LYMPHOCHANULOMA. Prophylaxis has been studied in this disease, both in vitro and in vivo (Rake). The only substances found to be effectual are certain arsenical drugs, including a number of those effectual against syphilis. Sulfonamides are ineffectual.

GONORRHEA. The available evidence to date rests almost entirely on in vitro experiments (Hill, Carpenter, Miller); and all combined in vitro and in vivo experiments, utilizing the chick embryo (Bang, Hill). These indicate that sulfonamides are perhaps effectual and that certain arsenical preparations are highly effective. As to the arsenicals, however, there is wide variation in results between different laboratories and, even from time to time, in the same laboratory.

There is in progress with a prospect of successful completion an experiment to transmit gonococcal infection to the immature vaginal membrane of young mice. This experiment has progressed far enough to indicate that the method will be useful in the testing of prophylactic agents.

GRANULOMA INGUINALE. No information.

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At this point the Chairman read a letter of September 9 from Dr. Herbert O. Calvery, which is in part quoted herewith, since it summarizes a great deal of information concerning the practical details of preparation of new prophylactic ointments. The letter follows:-

September 9, 1943.

Dear Dr. Moore:

As a result of a conference held in Col. Turner's office on June 21, 1943, ..... considerable work has been done in the further study of calomel ointments containing a sulfa drug, particularly sulfathiazole.....As a result of that conference, the ointment with the formula proposed by Dr. Thompson (now called SC-1003) has been issued by the Army for trial. (Because of the fact that this is a grease-base ointment, Dr. Thompson feels, and others of us agree, that it is not the most acceptable ointment that can be made available.) .....Col. Turner said yesterday that this formula has been found acceptable by the men. That means two important things.. namely, that it is not too irritating, and that its consistency, at least in summer temperature, is satisfactory.....

.....I felt that my subcommittee should get together, and in your absence I took it upon myself to call such a meeting. The meeting was held in New York on September 1, 1943, at 10 a.m. There were present Dr. W. S. Jones, Dr. Geoffrey Hake and Dr. W. G. Christiansen of E. R. Squibb and Sons, Dr. F.V. Sander and Mr. Robert Speagle of Ortho Products Co., Dr. Marvin Thompson of Warner Institute for Therapeutic Research, Mr. Geoffrey Woodard and myself of the Food and Drug Administration. In the opening remarks I briefly discussed the meeting in Col. Turner's office and then presented some of the requirements... for a venereal disease prophylactic ointment...(It must):-

1. be a one-tube prophylactic;
2. contain calomel and sulfathiazole (or some other selected sulfa drug;
3. be chemically stable, that is, the chemicals used must be compatible in the ointment base selected;
4. be thermostable;
5. have proper consistency, particularly over the range of temperature in which it will be used;
6. be nongreasy and cosmetically acceptable;
7. be nonirritating;
8. have good absorption characteristics;
9. be self-sterilizing or must have an acceptable germicide;
10. be odorless or contain an acceptable perfume.

.....We then presented the following outline for discussion..Under each of the headings and subheadings I am enclosing in parentheses a summary of the comments made with reference to the point in question.

I. Calomel-Sulfathiazole Ointment containing 30% calomel and 15% sulfathiazole.

(.....We had the impression, and this has since been confirmed, that .....sulfathiazole is...the drug of choice.).

A. Availability of component of ointment.

1. Quantity: Must be an amount sufficient to make 100 million to 150 million 5-gram tubes of ointment to meet a one-year supply for the Army, or approximately 20 million per month.  
(This means a requirement of approximately 1.3 million lbs. per year, or 100,000 lbs. per month, of total ointment; 30,000 lbs. of calomel per month, and 15,000 lbs. of sulfathiazole per month.)
2. Cost: The cost of the kit should not appreciably exceed that of the one now in use.
3. Priorities: Priorities should not be too difficult to obtain and the materials used in the preparation of the ointments should not be in too great competition with those used in other protective or therapeutic ointments requisitioned by the Army at the present time.

.....

B. Tube: Type, Characteristics and Availability

1. Metal
  - (a) Lead; lead with wax coat; lead with tin coat; lead with tin coat and wax coat; lead-tin alloy; lead-tin alloy with wax coat; pure tin; aluminum; lead with silver coat; and lead with silver and wax coat.
2. Plastic
3. Gelatin
4. Nozzle
  - (a) Length and taper
  - (b) Overall size and size of opening
5. Seams, crimp, cap: leakage and evaporation of moisture at these points.  
(This.....seemed to become a very important problem at the conference in Col. Turner's office. We therefore took it upon ourselves to make the tube and its characteristics a part of our investigation. Dr. Thompson did a considerable amount of work along this line and fortunately we were able .. in the Food and Drug Admin. to get Dr. Wiley and one of his associates, Dr. Rotondaro of the Drug Division, to aid us appreciably in these studies. As a result of the combined efforts of the two groups, a letter was sent to Col. Turner on August 4 giving the results of these investigations, copy of which was sent to you..... The complete details of Dr. Wiley's results are being incorporated as Section V of our C&R report this month. Our impression, from the data available at present, is that most any kind of metal tube can be used if it has a good wax coating. If the wax coating is not properly applied and leakage through it

should occur to the metal, the indications are that a lead tube or a lead with approximately 7-1/2% tin will be the best. Although the silver-lead tube was mentioned, none of us had had any experience with it. The plastic tubes studied were unsatisfactory and the gelatin tubes have already been considered unsatisfactory for other reasons. There has been suggested a new plastic tube called a Saran type with which Dr. Sander of Ortho Products is familiar and there has also been suggested to Col. Turner a plastic tube made of vinylite resin. The data available seem to indicate that there will be less loss of moisture and less leakage at seams and cap, etc., from the metal type tube than from any kind of plastic that may be available, but as stated above, the Saran and vinylite resin tubes have not been tested.

The consideration of the nozzle on the tube is a problem that will have to be answered by the clinicians. However, it was the consensus... that the nozzle on the present tube is too short and not sufficiently tapered. The size is approximately correct for the base of the nozzle and the size of the opening certainly should not be too small. It was the consensus..of the group that the nozzle should have a screw cap cover since the type cap which just slips on permits too much breathing and loss of moisture, leading to instability of the ointment.

### C. Physical-chemical characteristics

1. Particle size of the calomel and sulfa drug
2. Thermostability
3. Acceleration tests
4. pH
5. Cosmetic character
6. Consistency
7. Color
8. Odor
9. Osmosis
10. Buffer

(In the consideration of the particle size of the calomel and sulfa drug, the evidence indicates, and we were all agreed, that these should be micronized and the particle size be specified as not greater than 5 micra in diameter....Lumps should not be present.

Under thermostability we..agreed.... on an ointment that was stable over a range of 0 to 50°C and over this range maintained ointment consistency. ...However, ..an ointment will not be used with temperatures in this extreme range, particularly one at 0° since we feel that a preparation so far away from body temperature would be definitely irritating. Under this heading we considered that there should be no solid separation and no phase separation of the ointment.

.....Accelerated tests.... should continue for at least one month before final recommendation be made, and surveillance over much

longer periods should be maintained.....(Ointments) should be studied by maintaining them in tubes at constant heat from 50 to 55°, in cold storage at about -15°. They should have a 24-hr. alternating hot and cold treatment ranging from -15 to +50 to 55°. Some should be stored at room temperature,....defined as 25 to 35°.

....The consensus..was that efforts should be made to make an ointment with a pH of between 5.5 and 6.5.

With reference to its cosmetic character, the ointment should be smooth, free from tackiness, nongreasy vanishing cream type, and washable. It should have proper consistency for urethral injection, the color should be white and it should be odorless or have an acceptable perfume.

There was further discussion of the relative osmotic pressure and buffering capacity. The last two points were not too seriously considered but might be of physiological importance and in an attempt to attain perfection certainly should be considered.)

D. Physiological Characteristics

1. It should be nonirritating.

(....The question naturally arose as to what are the relative criteria of a nonirritating ointment and against what standards could its irritation be checked. It was agreed, of course, that preparations which have been used for urethral injection could be used as standards of reference, but these are relatively few and usually are solutions rather than ointments. In this laboratory and in some..others, the rabbit skin, eye and mucous membrane have been used for orientation purposes. In this laboratory also we have compared the relative irritation on the rabbit with that observed in the use of a patch test on the skin of man. The correlation is not too good and there are at times reversals, that is, something will be found to be relatively more irritating to the rabbit than to man and in other instances the relative irritation seems to be greater for man than for the rabbit. Consequently in a series of comparisons we do not find that the order of irritation for the series remains the same for the rabbit and for man. However, the rabbit is excellent for orientation purposes. We are obtaining as many commercial preparations as possible for relative comparisons. In this connection it has been gratifying to learn...that ointment SC-1003, now under test as an experimental ointment by the Army, has been found acceptable. The group felt that there was urgent need for available clinical material for simple irritation tests.....

2. Absorption

(Absorption of both the calomel and sulfathiazole should be good. Our definition of good is that it should be equal to or better than the absorption obtained from the present Navy base. The absorption

of calomel from the Navy base is about 1.3 times as great as that from the Army base. In a series of experiments in this laboratory we have tried breaking down the Navy base in order to find out what the component is which influences ..absorption... but as yet we have been unable to answer the problem. There are many bases ..satisfactory from the stability criteria, etc.,..from which calomel is better absorbed than (from) either the Army or Navy base, and there are many which can be prepared from which sulfathiazole would be much better absorbed than (from) either the Army or Navy base. However, when these two substances are put in the same base, ...the absorption of both is decreased, the specific reason for which we do not know. One could speculate on several possibilities. There are, however, few if any bases — in our experience only one— which failed to give as good absorption of calomel as the present Army base. All gave better absorption of sulfathiazole. The type of base which is most satisfactory from this standpoint of high-skin concentration, which will be discussed below, is the vanishing cream type of ointment. )

### 3. Skin concentration.

(It was the consensus.. that an ointment which would give relatively high skin concentration is preferred to one which did not give so high a skin concentration and first in preference should be one in which the high skin concentration paralleled good absorption. This again has been most frequently observed in vanishing cream type base).

### E. Bactericide

(The question was raised whether a bactericide was necessary and, if so, what type....In this connection Dr. Christiansen and Dr. Jores presented some data...on the amount of soluble mercury in several ointments.... In general the ointments in a base of the vanishing cream type contained a concentration of soluble mercury..of approximately 1 in 10,000. In some instances the concentration rose higher. In the grease-base ointments, the concentration was in general low..(A) concentration of soluble mercury salts ..(of) 1 to 10,000...is generally considered bacteriostatic but not necessarily bactericidal. In view of the presence of soluble mercury in these ointments, the group decided that for the present a bactericide was not indicated.)

### F. Surface-Active Agent

(The use of a surface-active agent was left open, depending upon the type of vanishing cream ointment selected. Many of the surface-active agents are quite irritating and do increase absorption, due primarily, we believe, to the fact that they are irritants. In some instances they may increase absorption by virtue of their wetting properties only, and not because of irritation. They should be used when indicated and the indications for use are increase in stability of the ointment, increase in wetting properties, increase in smoothness and applicability, and increase in absorption.)

II. New Types of Ointments.

(....The group felt that there were not available either the materials or the clinical data sufficient to justify immediate extensive study of ointments containing arsenicals, soluble mercury compounds, or highly bactericidal wetting agents. It was the unanimous opinion of the group that there was sufficient evidence for the adoption of a one-tube ointment and that every effort should be bent toward obtaining the most satisfactory one possible for immediate recommendation to the Army. On the basis of evidence already available, an ointment can be recommended which possesses most of the characteristics desirable as outlined above. The group was disappointed to learn of the results of Dr. Chesney who found that by the use of a vanishing cream calomel ointment he obtained no protection in 20 animals after a waiting period of four hours before inunction. However, they did not feel that these results should condemn the vanishing cream base for the following reasons:

1. The Army base which Dr. Eagle had previously used was not used as a reference for comparison.
2. The waiting period was four hours and the group did not have available the data on percentage protection that could be expected after four hours waiting period.
3. The particle size of the calomel used in the ointment was large, only 50% being less than 18 micra and 50% being 18 to 54 micra. ....Dr. Fleming, waiting one hour after inoculation before inunction, and using a calomel ointment with a particle size greater than 5 micra, found protection in only 9 out of 40 animals. Even though the particle sizes were equal and the waiting times were equal, the chances of Dr. Chesney's getting results that much different from Dr. Fleming by chance selection of animals is 1 in 25. Therefore, the inefficiency of the vanishing cream base is not proved. In our laboratory we have, with one exception as mentioned above, found that calomel absorption from the vanishing cream base is greater than from the Army base. In addition, in a high percentage of cases we have found the skin concentration from vanishing cream bases higher than from the Army base. We have used rabbits as did Dr. Chesney and therefore it seems to us that there must be some explanation for the lack of therapeutics other than simply the use of a vanishing cream base.

The group feels that an ointment similar to one of those listed below can be selected as most satisfactory for acceptance at the moment by the Army

.....

SC-1005 (440) - Calomel 30  
 Sulfathiazole 15  
 Spermacetti 3  
 Beeswax 0.67  
 Glycerol Monostearate 10.0  
 Propyl. Glycol 35  
 Duponol C 1.0  
 Water q.s. 100

SC-1003 (418) - Calomel 30  
 Sulfathiazole 15  
 White Petrolatum 40  
 Light Mineral Oil 14  
 Cetyl Alcohol 1

SC-2020 - Sulfathiazole 15  
 Calomel 30  
 Base 55 - composition of which is:  
 Propylene glycol 26  
 Starch glycerite 34  
 Stearic acid 4  
 Glycerol monostearate 2  
 Spermacetti 2  
 Water 32

Sincerely yours,

S/ Herbert O. Calvery  
Chief, Division of Pharmacology

\*\*\*\*\*

Colonel Turner then reported that a field trial had been undertaken with a 30 per cent calomel - 15 per cent sulfathiazole ointment in a fat base (SC-1003 of Dr. Calvery's letter- see above). Certain defects have been apparent in the large scale application of this ointment: 1) that the oil tends to separate out from the ointment; and (2) that the tubes have been unsatisfactory in certain mechanical details. It was felt that these defects in manufacture might be overcome if the contracting manufacturer would consult with Drs. Calvery and Thompson who developed the ointment for experimental use. Aside from the defects listed, the ointment has so far proved to be very satisfactory and no examples of irritation have been reported in several hundred cases in which it has been tried.

Considerable discussion ensued of the relative merits of the present Army petrolatum-lanolin base and a vanishing cream base. The latter is markedly superior in the major factor of absorption of both calomel and sulfathiazole. The chief difficulty with a vanishing cream base has to do with the loss of water which may occur in available tubes. It was felt, however, that this could be solved by the use of certain plastic tubes (vinylite -see comment in Calvery's

~~CONFIDENTIAL~~

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letter above), or in wax coated metal tubes.

Col. Turner pointed out that, in view of the present unsatisfactory state of Army prophylaxis, it is necessary for the Army to undertake a large scale field trial of the best ointment which can be evolved on the basis of present information; that the many years' background of use of calomel ointment and the experimental data available concerning it are such as to make it unjustifiable at present to drop calomel entirely in favor of arsenic; and that the Army might be able to conduct smaller experiments with other ointments than the one selected for large scale field trial.

On the basis of all of this discussion and of the promising experimental results obtained in the prophylaxis of syphilis and lymphogranuloma, the conference agreed on the following recommendations:

THAT AN ARSENIC -TEN PER CENT SULFATHIAZOLE\* OINTMENT CONTAINING INCREASING CONCENTRATIONS OF ARSENIC (VARYING BETWEEN 0.05 and 0.5%) BE PREPARED IMMEDIATELY IN TWO ALTERNATIVE BASES ( ONE VANISHING, ONE COLD CREAM); THE ARSENIC PREPARATION AND BASES TO BE SELECTED BY DRS. EAGLE, CALVERY, AND THOMPSON; THESE OINTMENTS TO BE SUBMITTED TO TRIAL FOR LOCAL IRRITATING EFFECT IN MAN BY TEN OR MORE VOLUNTEERS. IF THE OINTMENTS SELECTED PROVE TO BE NONIRRITATING, A FIELD TRIAL OF A REPRESENTATIVE OF THE SERIES SHOULD BE UNDERTAKEN BY THE U.S. ARMY.

The Conference also agreed to the following recommendation:

THAT THE U. S. ARMY CONTINUE THE FIELD TRIAL OF SINGLE TUBE PROPHYLACTIC OINTMENTS; THAT THE TRIAL OF A THIRTY PER CENT CALOMEL-FIFTEEN PER CENT SULFATHIAZOLE OINTMENT MADE UP BY THE FOLLOWING FORMULA:

CALOMEL	30
SULFATHIAZOLE	15
WHITE PETROLATUM	40
LIGHT MINERAL OIL	14
CETYL ALCOHOL	1

BE EXPANDED; THAT A SIMILAR OINTMENT IN THE FOLLOWING VANISHING CREAM BASE:

SULFATHIAZOLE	15
CALOMEL	30
BASE	55 - Composition of which is:
	Propylene glycol 26
	Starch glycerite 34
	Stearic acid 4
	Glycerol monostear-
	ate 2
	Spermacetti 2
	Water 32

\* The concentration of sulfathiazole is suggested at 10% because of information which has accumulated concerning the efficacy of this concentration in the prophylaxis of chancroid since the present Army experimental ointment containing 15% sulfathiazole was evolved in June 1943. There is reason to believe that 10% sulfathiazole will be as effective as 15%

BE GIVEN SIMULTANEOUS PRELIMINARY TRIAL; AND THAT IN ORDER TO ENSURE UNIFORMITY OF TRIAL METHOD AND THE ACCUMULATION OF ACCURATE DATA, THESE FIELD TRIALS BE PREPARED UNDER THE SUPERVISION OF AN OFFICER SPECIALLY DETAILED FOR THE PURPOSE BY THE SURGEON GENERAL

IN ORDER TO ENSURE A SATISFACTORY AND UNIFORM PRODUCT, THE MANUFACTURERS SELECTED TO PREPARE THESE OINTMENTS ON A COMMERCIAL SCALE SHOULD UTILIZE THE ADVICE OF DRS. CALVERY AND THOMPSON.

Finally the Conference agreed on the following recommendation:

THAT DR. JOHN F. MAHONEY BE REQUESTED TO GIVE IMMEDIATE EXPERIMENTAL TRIAL TO THE TWO OINTMENTS LISTED IN THE PRECEDING RECOMMENDATION IN THE PROPHYLAXIS OF GONORRHEA.

The Conference then adjourned.

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

*letter attached "Confidential"*

INSTITUTE FOR THE CONTROL OF SYPHILIS  
UNIVERSITY OF PENNSYLVANIA

PENNSYLVANIA STATE DEPARTMENT  
OF HEALTH COOPERATING

HOSPITAL OF THE UNIVERSITY OF  
PENNSYLVANIA, PHILADELPHIA

July 26, 1943.

Dr. T. R. Forbes,  
2101 Constitution Avenue,  
Washington, D.C.

Dear Dr. Forbes:

Enclosed herewith is a rough draft of the minutes of the meeting of the Conference on Biologic False Positive Serologic Tests which met in Washington on July 19, 1943. If I understand it correctly this Conference reports to the Subcommittee on Venereal Diseases, for approval of its acts and decisions before the acts and decisions are transmitted to the National Research Council as VD Subcommittee recommendations. If I am not in error on this point, I take it that you will withhold the formal transmission of the minutes to any other committees of the National Research Council until such time as the Subcommittee on Venereal Diseases has given its official approval.

In accordance with a request from Dr. Moore in a letter which I forgot to mention when I saw you in Washington, I am transmitting likewise a copy of my rough-draft minutes to Dr. Moore's secretary, who is requested also to refer them to Dr. Eagle in this particular case for any suggestions or corrections he may feel it advisable to make. I take it that the combination of Eagle's and my efforts will be cast into official form by Dr. Moore's secretary if I understand his letter correctly, and that copies will then go to the appropriate persons, doubtless including yourself, and certainly the membership of the Subcommittee on Venereal Diseases. It hardly seems worth while to me to consider calling a meeting of the Subcommittee on a matter of business of this sort in Dr. Moore's absence, but I should think that the finally drafted copy of the Conference proceedings could be sent to the individual VD Subcommittee members, read and approved by them; and if the majority approved, they could be regarded as accepted and recommended. If it seems advisable to have the Conference recommendations passed on in more detailed fashion, I suggest that the matter hold over until Dr. Moore's return.

Sincerely yours,

*John H. Stokes*  
John H. Stokes, M.D.

JHS;JVM  
Enclosure (draft of minutes)

*Will you complete the "Those present" list for Mrs. Giesko, Dr. Moore's Secy?*

Reports, Comm. Venereal Diseases -  
CONFIDENTIAL July 19, 1943  
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# CONFIDENTIAL

## RESOLUTIONS OF THE CONFERENCE ON BIOLOGIC FALSE POSITIVE SEROLOGIC TESTS FOR SYPHILIS

CONVENED BY THE DIVISION OF MEDICAL SCIENCES, NATIONAL RESEARCH COUNCIL

JOHN H. STOKES, M. D.  
TEMPORARY CHAIRMAN  
JULY 19, 1943

JUN 3 - 1965  
Medical  
DIVISION OF MEDICAL SCIENCES  
NATIONAL RESEARCH COUNCIL

INASMUCH AS a question has been raised as to the occurrence of biologic false positive serologic tests for syphilis following repeated donations of blood at certain Red Cross bleeding centers, the Conference was asked to consider the frequency and importance of this occurrence and its significance in relation to the program of investigation of biologic false positive serologic tests now under way.

### IT WAS RESOLVED THAT:

1. The problem of biologic false positiveness in syphilis from whatever cause seems of relatively small significance in the mass of material handled by the Red Cross.
2. Its influence in creating a wave of public reaction against blood donation can be dealt with most effectively by avoiding extended participation on the part of the Red Cross in a study of this problem beyond an inquiry addressed to donation centers as to frequency of positives in various donation groups, information to be transmitted to Dr. Stokes, Temporary Chairman, and Major Charles Rein, and a suggestion when possible that the person with an unsatisfactory blood go for further examination to a special consultant.
3. The study of the donation false positive problem should be set up on a smaller scale utilizing (a) prison groups, (b) Army Medical Laboratory participation, (c) Dr. Lund's laboratory. Further expansion shall be at the direction of a steering committee.
4. A steering committee for this study shall consist of Major Charles Rein, Chairman, Dr. Herbert Lund, Dr. Harry Eagle, Lieut. Barnard.
5. The Chairman, pro tem, of this Conference, Dr. Stokes, shall prepare a list of consultants for Red Cross centers to conduct examinations if desired, this list to be submitted to Dr. Canby Robinson for such use as the Red Cross organization may consider feasible and to Major Charles Rein.
6. The Red Cross will consider a mechanism for making blood from donors adjudged by special consultants to have false positive tests immediately available to the laboratories investigating the physical, bio-chemical and other problems of the syphilitic reagin.
7. Communications on this matter shall be rated "CONFIDENTIAL."

This document contains information affecting the national defense of the United States within the meaning of the Espionage Act, U.S.C. 50:21 and 32. Its transmission or the revelation of its contents in any manner to an unauthorized person is prohibited by law.

Don't mind  
per [unclear]  
24 Oct 1950

CONFIDENTIAL FILE -  
any Biological Laboratory

July 29, 1943

Mrs. Mason Gieske  
Secretary Dr. Moore  
604 Medical Arts Building  
Baltimore, 1, Maryland

Dear Mrs. Gieske:

Dr. John H. Stokes wrote me on July 26 regarding the minutes of the Conference on the Biologic False Positive Serologic Tests held in Washington on July 19, 1943, and sent me a copy of the draft of the minutes. I understand that you also received a copy of the draft which you will refer to Dr. Harry Eagle for corrections and suggestions and which you will then stencil and mimeograph.

As you will see from the enclosed copy of my letter of July 29 to Dr. Stokes, it is felt that the circulation of the minutes should be restricted to a very small group. If you will be kind enough to send me twenty-five copies of the minutes, we will be glad to attend to their circulation from this office.

I suggest that the minutes be headed "CONFERENCE ON BIOLOGIC FALSE POSITIVE SEROLOGIC TESTS." The general arrangement of the minutes should conform to that used in the past. Each page of the minutes should be marked "CONFIDENTIAL."

On Page 7 the second paragraph should read: "A series of resolutions was then drafted; a copy is appended. They were passed unanimously." The remainder of this paragraph should be deleted.

The following paragraph lists the persons present:

Those present were: Dr. John H. Stokes, Chairman; Drs. Joseph Beard, Bernard Davis, and Herbert Lund; for the NRC-CMR, Capt. Cushing, Dr. Andrus, ~~Spencer~~ and Forbes; for the Army, Lt. Colonel T. B. Turner and Major Charles Bell; for the Navy, Lieut. (jg) R. D. Turner; for the USPHS, Drs. Harry Eagle, John Mahoney, and Ad Harris; for the American Red Cross, Dr. G. Canby Robinson.

I appreciate very much your stenciling and mimeographing this and other minutes which you have taken care of in the past. This assistance is a real help. Please let me know if any questions arise.

Very truly yours,

T. R. Forbes, for  
Division of Medical Sciences

Enclosure  
TDF:pr

Copies to Dr. J. H. Stokes

~~CONFIDENTIAL~~

Indexed

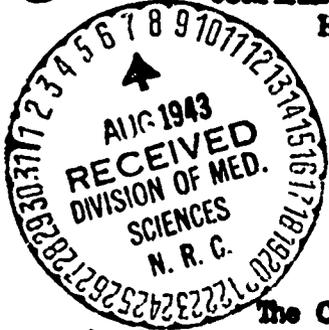
MINUTES  
OF A

CONFERENCE ON BIOLOGIC FALSE POSITIVE SEROLOGIC TESTS FOR SYPHILIS  
Held under the auspices of the Subcommittee on Venereal Diseases  
NATIONAL RESEARCH COUNCIL

in  
Washington, D.C. July 19, 1943

Under the temporary chairmanship of  
Dr. John H. Stokes, for the Subcommittee  
on Venereal Diseases, Medical Division.

NOT FOR PUBLICATION  
WITHOUT PERMISSION OF  
NATIONAL RESEARCH COUNCIL



The Conference met at 10 A.M. July 19, 1943, in the Reading Room of the Academy of Sciences Building, 2101 Constitution Avenue, Washington, D.C.; the conferees present were: Dr. John H. Stokes, Chairman, Dr. Herbert Lund, Dr. J. W. Beard, Dr. Bernard Davis; from NRC-CMR Capt. E. H. Cushing, Dr. E. C. Andrus, Dr. Sprague, Dr. T. R. Forbes; from the U.S. Army, Lt. Col. T. B. Turner and Major Charles Rein; from the U. S. Navy Lieut. (j.g.) R. D. Turner; from the U.S. Public Health Service Dr. Harry Eagle, Dr. John F. Mahoney, and Dr. Ad Harris; from the American Red Cross Dr. G. Canby Robinson.

The meeting was convened by Dr. J. E. Moore (absent) to consider reports of biologic false positive serologic tests for syphilis following repeated blood donations. Other items of business concerning the work of the Conference were subsequently considered.

The meeting was opened by a reading into the record of observations by Dr. J. E. Moore on 93 blood specimens run within a period of two weeks from multiple donors at the American Red Cross center at Baltimore.

One	of	these	had	given	3	donations
One	"	"	"	"	4	"
38	"	"	"	"	6	"
30	"	"	"	"	7	"
15	"	"	"	"	8	"
8	"	"	"	"	9	"

Of these, two were strongly positive. One was weakly positive with a sone reaction in the Wassermann; the other was doubtful. Twenty-two were negative to all flocculation tests but anticomplementary with the Wassermann. The remainder were negative throughout.

This was followed by the reading, with Dr. Davis' approval, of a letter from Dr. Davis to Dr. Moore on this subject, dated July 14, 1943, as follows:-

~~This document contains information affecting the national defense of the United States within the meaning of the Espionage Act, U.S.C. 80; 81 and 82 its transmission or the revelation of its contents in any manner to an unauthorized person is prohibited by law.~~

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Dr. J.E. Moore  
Baltimore, Maryland.

July 14, 1943.

Dear Dr. Moore:

As suggested in your letter of June 30, 1943, I have been inquiring at local bleeding centers concerning the possibility of finding biologic false positives among multiple blood donors.

At Presbyterian Hospital, Dr. Scudder informs me that they have very few multiple donors in their blood bank and have not noted the phenomenon.

At the Red Cross, Dr. Weiss informs me that they have not noted any appreciable incidence of positive tests in repeat donors. When such tests have been encountered, their procedure has been to follow the usual routine of recommending that the donor consult his physician. In this way, they have no clinical records to lead to a suspicion that any given test is false.

The largest set of data applicable to the problem were those found at the Blood Transfusion Association. This is an organization which furnishes professional donors. Before blood banks came into common use they furnished up to 900 donors a month to hospitals and physicians, and for the last few years they have been running 150 to 200 a month. They have had a total of perhaps 5000 donors in their 15 years of service, most of whom have given a number of transfusions at rather frequent intervals before dropping out of sight. I saw the records of 115 men who had given from 10 to 40 liters of blood over a course of a number of years. All their donors are given a Kahn test before being sent out on any call, and the City Board of Health gives them an annual Wassermann test in issuing their professional blood donor's book. While they had no readily available data on the incidence of positive tests among their donors, they could hardly remember that any of their repeated donors had been dropped from the list for this reason, and felt that the incidence was of the order of magnitude of one case a year. In no case had the question of a false positive test been raised.

I am thus unable to confirm your interesting observation, and while the experience of the Blood Transfusion Association does not rule out its validity, it makes it seem unlikely that it is a problem of great magnitude. I also cannot readily accept the argument linking the phenomenon with the increased synthesis of G-2. As we know, any of these chemical fractions contains innumerable chemical species, and while the false positive reactions may be due in some cases to some abnormal substance found in fraction G-2, it does not follow that an increase in the proportion of normal G-2 in a serum should lead to a false positive test. If such were the case, the G-2 fractions from negative sera would be expected to be positive in sufficiently high concentration.

Sincerely,

S/ Bernard Davis  
Neurological Institute, New York."

Commenting on this letter, Dr. Davis emphasized the experience of the Blood Transfusion Association which he felt rather strongly confirmed the impression that biologic false positiveness from multiple donation as such, must be an extremely rare phenomenon if it exists at all.

Major Charles Rein then gave a summary of some observations on the possibility of a positive serologic reversal after blood donation, based on studies of blood specimens from the Red Cross Blood Donors' Center at Columbus, Ohio, referred to the Division of Serology at the Army Medical School. To the date of reporting, 14 instances had occurred in which previously serologically negative blood donors at the Columbus Center had shown some degree of serologic positivity after the withdrawal of 500 c.c. of blood. In 3 instances in this category there had been temporary rejection from service in the Armed Forces of individuals who were serologically negative at the time of their donations, and subsequent to these donations were found to have positive serologic reactions. In two of these instances there was corroborative evidence of the original serologic negativity and no other factor ordinarily recognized as being conducive to biologic false positives could be uncovered. The tests turned negative, in time, and induction into the Armed Forces has taken place. A third instance in this category is now being observed. It was estimated that of 51,107 original donors, 0.354 percent had been serologically positive under all categories. Of 21,000 re-donors on second donation, 0.091 have been serologically positive. Of 1,689 repeat re-donors (third donation) 0.236 percent had been seropositive. The case of a female, age 21, was described, as an instance of apparent false positive serologic test after blood donation. It was concluded that the material indicated there was some possibility that the withdrawal of blood to the extent that is practiced for blood donations for blood transfusion may influence subsequent blood samples to the extent that a previously masked seronegative lues may revert to a seropositive form, and also that such bleeding may cause the appearance in subsequent samples of a degree of false biologic positivity of such extent as to subject the nonsyphilitic individual to considerable annoyance and inconvenience. Major Rein verbally recited six possible explanations for false positive reactions following blood donation, as follows:-

- (1) Regeneration of globulin fraction (G-2).
- (2) Technical error; false positive report on first specimen.
- (3) Reactivation of an old syphilis.
- (4) Intercurrent nonsyphilitic disease between donations.
- (5) First blood taken during the primary incubation stage (seronegative stage of syphilis).
- (6) Development or acquisition of syphilis between the first and second donations.

Dr. Lund stated that in the examination of 500 Red Cross bloods which he had conducted by his special method, using 2 c.c. of serum, first donors gave 43 percent false positives (recall the large amount of serum used); second donors 46 percent; and third donors, 52 percent. An apparent increase in the proportion of false positives with increased donations. Dr. Lund stated that the reacting substance responsible for the false positive seemed more common in females, and that there was a suggestion that females returned more frequently for multiple donations.

Dr. Canby Robinson was then requested to present the point of view of the Red Cross on the problem. He stated that in collecting blood from voluntary donors, the Red Cross stood in a difficult public relation in which the occurrence of local embarrassing situations might have wide repercussions. It is Red Cross policy to avoid complicating doctor-patient relationships, and for that reason the patient on whom a serologic positive (3 plus or 4 plus) was recognized from the donated blood, was contacted by a series of letters, the first of which states that the blood is "unsatisfactory". A second and a third letter calling the donor's attention to the situation is then sent and if no response to the third letter is obtained, the donor's name is finally reported to the State Department of Health. Medical heads of donor centers are instructed to be very circumspect in their dealings with patients on these matters, and great care and tact are necessary to avoid creating an embarrassing local situation or stirring up trouble through physician-patient relationships. Dr. Robinson stated, however, that it would be entirely possible for the Red Cross to go back over its records, and identify multiple donors from its lists to ascertain whether there was an increased proportion of serologic positives for syphilis (true or biologically false) in the Red Cross material. He expressed the personal opinion that the biologic false positive could not be very common over the country at large, but expressed a willingness to go into the problem.

In response to questions it was brought out that the serologic tests are done by the serologic laboratories of the processing pharmaceutical firm. The blood, when obtained, is refrigerated locally; then transferred to a Church container at a temperature of 2 to 10 degrees Centigrade. The blood reaches the laboratory within 24 to 72 hours from the time of drawing to the time of centrifuging. The blood in the rubber tube attached to the needle is the fraction of the specimen which is used for serologic tests. Bloods showing weak positives are rechecked in the laboratory performing the original test. A 2 plus complement fixation reaction on re-test rates the blood as unsatisfactory, but a 1 plus or 2 plus precipitation test on re-check may be processed as satisfactory. A re-check on 3 plus and 4 plus bloods before returning reports of "unsatisfactory" is requested of the processing laboratory where possible, but in any event, the report of "unsatisfactory" is expected to show whether or not a re-test has been done. The local Red Cross Center director does not have power even to insist that a donor with an unsatisfactory blood have a re-test serologic test on a new specimen.

In open discussion the trend of opinion appeared to be that, granted there was a suggestion that multiple blood donation might give rise to authentic biologic false positive tests, the problem in the aggregate and from the practical standpoint for the Red Cross was not a serious one. It appeared, therefore, that the problem might be separated into two parts -- one, the policy and administrative issue of the seriousness of such an effect and publicity in regard to it on the willingness of the public to donate blood to the Red Cross; and the other, the merits of the question of biologic false positiveness induction by bleeding as such. It was felt that the problem was a biological one of a highly complicated nature, involving many control factors which would necessitate setting it up, at least at the start, as a small scale experiment on a limited group of persons donating blood repeatedly solely for the purpose of determining the effect in producing biologic false positives. It was deemed inadvisable to attempt to collect such blood or the blood of multiple donors

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for such studies through the Red Cross, unless after conference and consideration, the Red Cross felt that such a contribution was possible without creating embarrassing local situations. Since the problem was estimated as being numerically of small magnitude, the feeling was that the Red Cross organization would be wise to ignore it, at least for the time-being, standing by a positive statement as to the harmlessness of donating blood for transfusion rather than any qualifying or inferentially committal statement regarding possible biologic false positive tests.

In order to set up the small-scale study of the alleged phenomenon under proper direction, it was agreed that a Subcommittee of the Conference, consisting of Doctors Eagle, Lund, and Barnard with Dr. Rein as Chairman, should assume the responsibility of organization, utilizing in all probability the Columbus Center which has already shown a decided interest in the problem. Meanwhile, on submission of the appropriate resolutions (see below) to the Red Cross, Dr. Robinson and his associates would consider checking back over Red Cross records of multiple donors and also the question of furnishing limited supplies of multiple donor blood for study. Dr. Robinson emphasized the desire of the Red Cross to be fully cooperative in these matters.

A series of resolutions was then drafted; a copy is appended. They were passed unanimously.

The Conference then took up a suggestion as to further procedure with regard to donation false positives made by Dr. J. E. Moore in a letter to Dr. Stokes, dated July 16th, 1943, as follows:

"The idea which I suggested to you briefly over the telephone (is as follows:0

"This is, that in the event that this phenomenon of positive blood tests after repeated donations is observed in other locations than Baltimore, Washington, and Detroit where it has so far apparently been observed, would the Red Cross be willing to consent to setting up in a number of cities designated 'consultants' to whom such persons might be referred for an evaluation of the positive test. Offhand I would suggest that appropriate places and consultants might be as follows:- (an incomplete list was given) ...

"It seems to me essential that an arrangement be made whereby a careful and so far as possible identical historical, physical, and serologic work-up of such persons be carried out in order to determine whether we are actually dealing with false positive tests, with infections of syphilis occurring after the initial test, with reactivations of old syphilis, or with any other of the several possibilities which occur to one offhand. It seems to me also necessary that such persons be examined free of charge to them unless and until, of course, it becomes obvious that they have syphilis, in which case the patient may be either continued with the consultant to whom the Red Cross referred him, or report to his own physician and pay for his medical care.

"If the experience of other cities is likely to parallel that of Baltimore in which we have seen perhaps 6 or 8 such cases a month, the question might also be discussed as to whether these detailed examinations should be paid for on a research basis either by the American Red Cross, OSRD, or the United States Public Health Service.

"Finally, if Dr. Robinson is willing to agree to such a procedure as this, it seems to me perhaps desirable that a committee of three consisting of you (Stokes), Robinson and myself, or in my absence, Charles Rein, be set up in order to outline the detailed study to which such patients should be subjected by a consultant."

After discussion it was agreed that the temporary chairman, Dr. Stokes, should supply a list of possible consultants on the evaluation of individual cases at the cities listed in the official enumeration of Red Cross Donor Centers throughout the United States. After this list is supplied to Dr. Robinson, he will take up with his executive colleagues at the Red Cross the question of developing such a mechanism as Dr. Moore has suggested.

Meanwhile, the subcommittee of the Conference chairmanned by Dr. Rein, which will set up the direct investigation of the biologic false positive question in multiple donations, will select a local consultant to control the clinical side of the special investigations as and wherever they are conducted.

The Conference then took up the question of obtaining more, and more satisfactory blood specimens for the study of biologic false positiveness in general. Doctors Beard and Davis recited the difficulties which they have had in obtaining specimens and cooperation from sources which they have approached. In a general discussion it was agreed that blood donations from inoculation malaria volunteers would constitute the ideal material for a study of the mechanism of biologic false positiveness due to other diseases than syphilis. It was indicated that such voluntary donors could be selected with a view to the thorough-going exclusion of a previous syphilitic infection in the donor before he underwent malarial inoculation; that he could, if under satisfactory control, have a blood specimen examined serologically daily in the laboratory until such time (expected incidence 100 percent) as he became falsely positive under the influence of his inoculation malaria. Then a larger specimen amounting to a donation of 300 to 400 c.c. could be drawn, shipped to the special investigating centers under controlled conditions, and studied for the globulin fraction and so forth.

At this point Dr. Forbes suggested that Dr. Andrus be called, and Dr. Andrus was given a review of the problem in order that he might consider the feasibility of inviting the participation of conscientious objectors under the direction of Selective Service in the volunteer work. Dr. Andrus was unable to contact the appropriate officials of Selective Service during the meeting.

Dr. Davis stated that if a group of chosen donors could be assembled at any point within reasonable distance of his base of operations, he would be glad

~~CONFIDENTIAL~~

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to assume entire medical charge of the problem, caring for the patients as such, as well as directing the laboratory studies.

Dr. Andrus stated that he would report to Dr. Stokes as soon as possible the attitude of Selective Service on the question of the participation of conscientious objectors in this work.

There being no further business to come before the Conference, the meeting adjourned.

John H. Stokes, M.D.

Acting Chairman  
Subcommittee on Venereal Diseases,  
National Research Council.

~~CONFIDENTIAL~~

RESOLUTIONS OF THE CONFERENCE ON BIOLOGIC FALSE POSITIVE  
SEROLOGIC TESTS FOR SYPHILIS  
CONVENED BY THE SUBCOMMITTEE ON VENEREAL DISEASES

JOHN H. STOKES, M.D.  
TEMPORARY CHAIRMAN  
JULY 19, 1943.

INASMUCH AS a question has been raised as to the occurrence of biologic false positive tests for syphilis following repeated donations of blood at certain Red Cross bleeding centers, the Conference is asked to consider the frequency and importance of this occurrence and its significance in relation to the program of investigation of biologic false positive tests now under way.

IT WAS RESOLVED THAT:

1. The problem of biologic false positiveness in syphilis from whatever cause seems of relatively small significance in the mass of material handled by the Red Cross.
2. Its influence in creating a wave of public reaction against blood donation can be dealt with most effectively by avoiding extended participation on the part of the Red Cross in a study of this problem beyond an inquiry addressed to donation centers as to frequency of positives in various donation groups; information to be transmitted to Dr. Stokes, Temporary Chairman, and Major Charles Rein; and a suggestion when possible that the person with an unsatisfactory blood go for further examination to a special consultant.
3. The study of the donation false positive problem should be set up on a smaller scale utilizing (a) prison groups, (b) Army Medical Laboratory participation, (c) Dr. Lund's laboratory. Further expansion shall be at the direction of a steering committee.
4. A steering committee for this study shall consist of Major Charles Rein, Chairman, Dr. Herbert Lund, Dr. Harry Magle, and Lieut. Barnard.
5. The Chairman, pro tem, of this Conference, Dr. Stokes, shall prepare a list of consultants for Red Cross centers to conduct examinations if desired; this list to be submitted to Dr. Conby Robinson for such use as the Red Cross organization may consider feasible, and to Major Charles Rein.
6. The Red Cross will consider a mechanism for making blood from donors adjudged by special consultants to have false positive tests, immediately available to the laboratories investigating the physical, bio-chemical and other problems of the syphilitic reagin.
7. Communications on this matter shall be rated "CONFIDENTIAL".

MINUTES OF A CONFERENCE ON THE  
INTENSIVE ARSENOTHERAPY OF EARLY SYPHILIS  
Held under the auspices of  
the

Subcommittee on Venereal Diseases of the  
National Research Council  
in

Washington, D. C.

May 19, 1943

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WITHOUT PERMISSION OF  
NATIONAL RESEARCH COUNCIL

On May 19, 1943, there was held at the National Academy of Sciences under the auspices of the Subcommittee on Venereal Diseases a conference on intensive arsenotherapy of early syphilis.

Present were the following:

- From the Subcommittee on Venereal Diseases Doctors J. E. Moore, John H. Stokes, and Walter Clarke.
- From the Committee on Medicine Dr. O. H. Perry Pepper.
- From the National Research Council Doctors Lewis Weed, T. R. Forbes, G. K. Anderson, and Owsei Temkin.
- From the Committee on Medical Research Dr. George Guest.
- From the U. S. Army Col. Alden Freer, Lt. Col. R. G. Prentiss, Lt. Col. F. R. Dieuaide, Lt. Col. T. S. Turner, Maj. Robert Dyar, Maj. Thomas L. Sternberg, Maj. Donald L. Rose, and Capt. William Leifer.
- From the U. S. Navy Capt. W. W. Hall, Lt. Comdr. W. H. Schwartz, and Lt. Howard Ennes.
- From the U. S. Public Health Service Doctors Otis L. Anderson, W. G. Workman, and Harry Eagle.
- From the Royal Canadian Air Force Flight Lieutenant B. Leibel,

and the following interested persons: Doctors H. T. Hyman, Arthur Schoch, George W. Bowman, Evan V. Thomas, and L. W. Shaffer.

The Chairman opened the meeting with a brief discussion of the present status of intensive arsenotherapy, pointing out that complete and incomplete data were now available on some 10,000 persons with early syphilis treated by one or another modification, in which the duration of treatment ranged from one day to 12 weeks. The available methods are broadly divisible into two general groups: one, those which seek to compress chemotherapeutic treatment into two weeks or less, with or without the addition of fever therapy; and those which, relying on chemotherapy alone, occupy a period of 6 to 12 weeks. The mortality rates of the two broad general systems are now fairly definite on the basis of large series of patients. In the short treatment systems the mortality rate ranges consistently around 1 in 200 to 1 in 300 persons treated. In the longer intensive systems the mortality rate is of the general order of 1 in 1500 to 1 in 2000 persons treated. Insofar as now can be determined from available information, which is admittedly incomplete with regard to the longer systems, the therapeutic results in terms of "cure" and "unsatisfactory results," the latter including clinical and serologic relapse and seroresistance, appear to be essentially identical.

The Chairman further pointed out that on the basis of this information the Subcommittee on Venereal Diseases has already expressed itself as believing in principle that information concerning the intensive arsenotherapy of early syphilis is now sufficiently adequate to justify recommending its adoption by the Armed Forces under certain selected circumstances.

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After full discussion the Conference approved the following recommendations:

I. OWING TO THE RELATIVELY HIGH MORTALITY RATE, NO SYSTEM OF INTENSIVE ARSENOTHERAPY COMPRESSED INTO A PERIOD OF TWO WEEKS OR LESS IS AS YET SUITABLE FOR ROUTINE ADOPTION BY THE ARMED FORCES.

II. FOR THE ROUTINE TREATMENT OF EARLY SYPHILIS IN THE ARMED FORCES THE TWENTY-SIX WEEKS' SYSTEM NOW IN USE IN THE U. S. ARMY SHOULD BE CONTINUED PENDING FURTHER INFORMATION CONCERNING INTENSIVE TREATMENT SYSTEMS.

III. IT IS HOPED THAT THE U. S. PUBLIC HEALTH SERVICE WILL AMPLIFY A STATISTICAL EVALUATION OF THE SEVERAL METHODS OF INTENSIVE ARSENOTHERAPY OF EARLY SYPHILIS (RANGING FROM ONE DAY TO TWENTY-SIX WEEKS' SYSTEMS); THIS STUDY TO INCLUDE ESPECIALLY DATA AS TO MORTALITY AND MORBIDITY RATES AND CLINICAL AND SEROLOGIC RESULTS; AND TO BE BASED INsofar AS POSSIBLE NOT ONLY ON CASES CURRENTLY UNDER TREATMENT UNDER U. S. PUBLIC HEALTH SERVICE AUSPICES, BUT ALSO ON CASES ALREADY TREATED BY VARIOUS INDEPENDENT INVESTIGATORS. AN EARLY EVALUATION OF MORBIDITY AND MORTALITY IS PARTICULARLY DESIRED. IT IS REQUESTED THAT THE DATA SO GATHERED BY THE U. S. PUBLIC HEALTH SERVICES BE MADE CURRENTLY AVAILABLE TO THE SUBCOMMITTEE ON VENEREAL DISEASES, NATIONAL RESEARCH COUNCIL.

IV. IN OVERSEAS AREAS, WHETHER ADVANCED TRAINING OR COMBAT ZONES, NO ALTERNATIVE METHODS OF INTENSIVE ARSENOTHERAPY OF EARLY SYPHILIS, TREATMENT COMPRESSED WITHIN A PERIOD OF TWO WEEKS OR LESS, MAY BE UTILIZED PROVIDED:

a) THAT PATIENTS BE TREATED UNDER HOSPITALIZED CONDITIONS RATHER THAN ON AN AMBULATORY BASIS; AND

b) THAT TREATMENT BE ADMINISTERED UNDER THE DIRECTION OF SPECIALLY QUALIFIED PERSONNEL.

THESE SAME INTENSIVE TREATMENT SYSTEMS MAY ALSO BE UTILIZED IN CONTINENTAL UNITED STATES IN SELECTED PERSONNEL, SUBJECT TO THE SAME QUALIFICATIONS AS (a) AND (b) ABOVE.

IT IS DESIRABLE THAT THE RELATIVE RISKS OF INTENSIVE VERSUS PROLONGED METHODS OF TREATMENT BE EXPLAINED TO THE PATIENT.

ATTENTION IS CALLED TO THE FACT THAT TO HOSPITAL CENTERS IN WHICH INTENSIVE ARSENOTHERAPY IS ADMINISTERED THERE IS, OR WILL SHORTLY BE, AVAILABLE A COMPOUND, THE CODE NAME OF WHICH IS \_\_\_\_\_, WHICH MAY PROVE TO BE OF VALUE IN THE TREATMENT OF ARSENIC POISONING.

THE TWO METHODS OF INTENSIVE ARSENOTHERAPY RECOMMENDED FOR HOSPITAL USE IN ACCORDANCE WITH THE PARAGRAPHS ABOVE ARE:

1. THE FIVE DAY INTRAVENOUS DRIP
2. A TEN DAY MULTIPLE SYRINGE TECHNIQUE.

THE EXACT DETAILS OF THESE TECHNIQUES PREPARED BY A SUBGROUP CONSISTING OF DR. EVAN THOMAS, ARTHUR SCHOCH, GEORGE W. BOTMAN, AND CAPTAIN WILLIAM LEIFER, ARE APPENDED HEREWITH AS EXHIBIT "A".

V. IN THE EVENT THAT HOSPITALIZATION IS NOT PRACTICABLE FOR PATIENTS WITH EARLY SYPHILIS IN OVERSEAS AREAS OR IN THIS COUNTRY, A MODIFIED INTENSIVE TREATMENT SCHEME OCCUPYING A TWELVE WEEKS' PERIOD MAY, IN SELECTED CASES, BE SUBSTITUTED FOR THE TWENTY-SIX WEEKS' SCHEME WHICH IS NOW STANDARD IN THE U. S. ARMY. WITH THE TWELVE WEEKS' SYSTEM PATIENTS MAY BE TREATED ON AN AMBULATORY BASIS AND WITH THEIR UNITS.

AN EXACT DESCRIPTION OF THE TWELVE WEEKS' SYSTEM PREPARED BY DR. HARRY EAGLE IS APPENDED HEREWITH AS EXHIBIT "B".

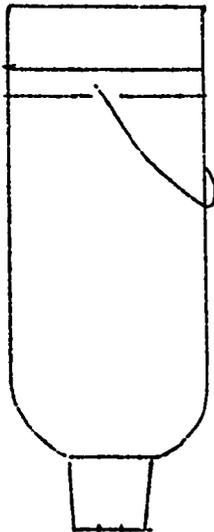
VI. THE ABOVE RECOMMENDATIONS AS TO INTENSIVE ARSENOTHERAPY APPLY ONLY TO PATIENTS WITH EARLY SYPHILIS WHO HAVE RECEIVED NO PREVIOUS TREATMENT, OR PRACTICALLY NONE, AND DO NOT APPLY TO PATIENTS WITH LATE LATENT OR VARIOUS FORMS OF LATE SYPHILIS.

At 3:00 P.M. the meeting adjourned.

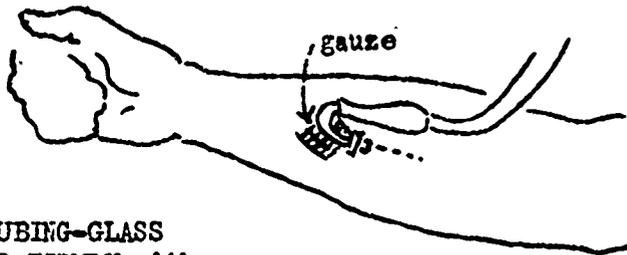
2000 cc vacuum packed  
(standard) flask of  
5% dextrose in normal  
saline solution

2½-3 feet above level  
of arm.

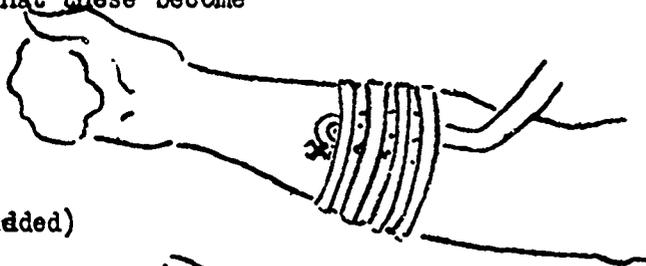
SITE OF INJECTION  
Needle inserted to hub  
between elbow and wrist



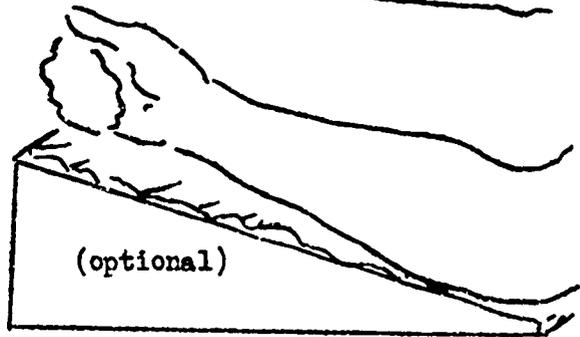
ARRANGEMENT OF DRIP  
after insertion  
of needle



NEEDLE HUB-TUBING-GLASS  
ADAPTER TAPED FIRMLY with  
adhesive so that these become  
A PART OF  
FOREARM



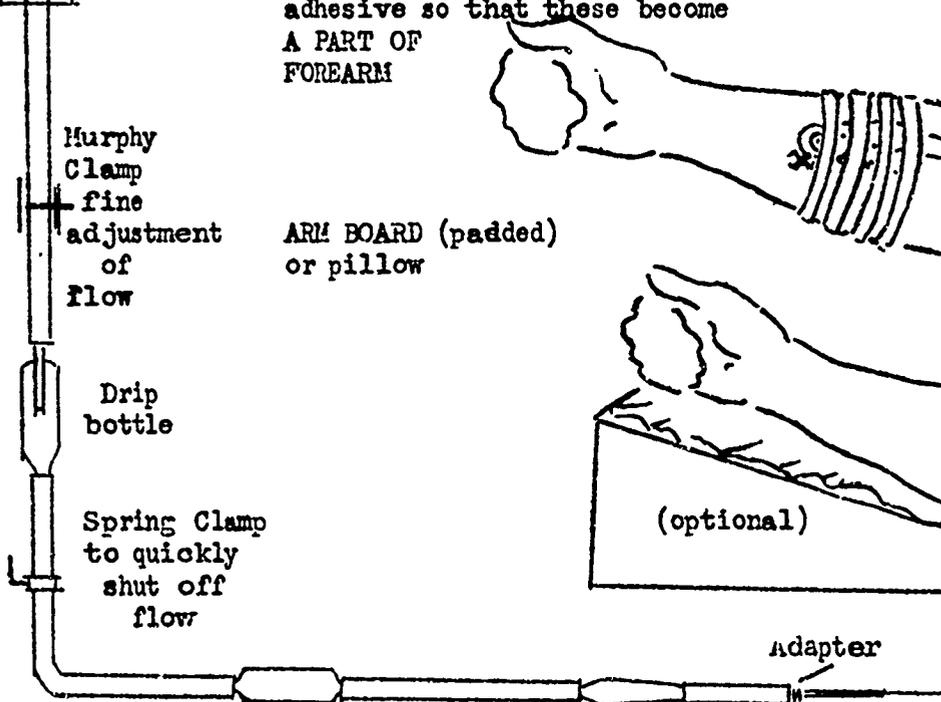
ARM BOARD (padded)  
or pillow



Murphy  
Clamp  
fine  
adjustment  
of  
flow

Drip  
bottle

Spring Clamp  
to quickly  
shut off  
flow



adapter  
Finer  
rubber  
tubing  
20 gauge  
1½" needle

## THE INTENSIVE ARSENOTHERAPY OF EARLY SYPHILIS:-

### DESCRIPTION OF METHODS.

#### INDICATIONS

All methods of intensive arsenotherapy described below are limited to the treatment of patients with early syphilis, i.e., primary and secondary syphilis, relapsing secondary syphilis, and early latent syphilis (i.e., latent syphilis of not more than one year's duration), who have received no previous treatment or practically none.

#### CONTRAINDICATIONS TO ALL METHODS

In patients with serious visceral disease, such as hepatitis, myocarditis, severe hypertension, nephritis, excessive alcoholism, blood dyscrasias, active pulmonary tuberculosis, history of previous serious arsenical idiosyncrasy, etc., intensive arsenotherapy should not be employed.

Sulfonamide therapy for gonorrhea or other conditions and 5-10 day intensive arsenotherapy should not be given simultaneously. There is, however, no objection to the combination of sulfonamides with the 12 week treatment system (see below).

#### THE MORTALITY RATE FROM INTENSIVE ARSENOTHERAPY

Death from intensive arsenotherapy is usually due to the serious reaction of toxic encephalopathy (see below). Excluding the possibility of the successful treatment of this and other serious reactions by a new secret compound (see below), the risk of death is directly proportional to the duration of treatment, i.e., the shorter the period in which the average total dose of 1200 mgm. mapharsen is given, the higher the mortality.

With either the 5-day intravenous drip or the 10-day multiple syringe injection methods herein described, the incidence of toxic encephalopathy is about 1 in 100 patients treated, and the mortality rate about 1 in 200 to 1 in 300 patients treated.

With the modified intensive 12-week schedule described below, the incidence of toxic encephalopathy is about 1 in 1500 patients treated, and the death rate about 1 in 1500 to 1 in 2000.

With the standard Army 26-week treatment system, toxic encephalopathies practically disappear, and the death rate from treatment is less than 1 in 5000 patients treated.

These mortality rates for intensive arsenotherapy are, however, qualified somewhat for Army practice by the fact that in civilian life, the majority of serious reactions and of deaths have occurred in women.

PRE-TREATMENT ROUTINE (ALL METHODS OF INTENSIVE ARSENOTHERAPY)

1. Complete physical examination.
2. Laboratory studies.
  - a. Diagnostic (darkfield and STS\*, quantitatively titred, if possible).
  - b. Urine analysis (specific gravity, acidity, albumin, sugar, microscopic).
  - c. Complete blood count (hemoglobin, red blood cell, white blood cell and differential count).
  - d. Other laboratory procedures are done only on indication.

TECHNIQUE OF 5-DAY INTRAVENOUS DRIP

Apparatus Required:- 1. Vacuum-packed flasks containing 2000 cc. of 5% dextrose preferably in normal saline solution (or 5% dextrose in sterile distilled water), accompanied by the usual tubing, drip chamber, clamps, observation window and adapter for needle.

2. Intravenous needle of approximately 20 gauge and 1-1/2 inch length.
3. Adhesive tape or scotch electric tape (1/2 inch width).
4. Ampoules mapharsen\*\*, of 0.04 gm., 0.06 gm., and 0.6 gm. capacity.

Dosage of Mapharsen:- 1. Total dosage for the five day treatment period is determined by the stripped weight of the patient, in patients weighing less than 70 kg. (155 lbs.), the total dose is 1000 mgm. (1.0 gms.); in those weighing 70 kg. (155 lbs.) or more, the total dose is 1200 mgm. (1.2 gms.).

2. The daily dose is 200 mgm. (0.2 gm.) for patients receiving a total of 1000 mgm. (1.0 gm.).

3. The daily dose is 240 mgm. (0.24 gm.) for patients receiving a total of 1200 mgm. (1.2 gm.).

4. If a patient receives less than the intended daily dose (this will most often occur on the first day of therapy), the deficiency in dosage may then be spread over the remaining days of treatment. Thus, if the patient receives 120 mgm. (0.12 gm.) the first day instead of the intended total daily dosage of 240 mgm. (0.24 gm.), he may be given 30 mgm. (0.03 gm.) additional on each of the succeeding 4 days of treatment.

Procedure of Intravenous Drip:- 1. Dissolve the total daily dose of mapharsen in 10 cc. of sterile distilled water and insert this solution under sterile precautions into the dextrose solution contained in the vacuum-packed flask.

\*STS \* Serologic test for syphilis.

\*\*The mapharsen brand of phenarsine hydrochloride (other phenarsine hydrochlorides are available on the open market).

2. The needle is attached to a 2 cc. Luer-type syringe for ease of handling and recognition of successful venepuncture.

3. Select a vein on the forearm, preferably between the wrist and the elbow; any aspect may be used but the volar aspect is most comfortable. The introduction of the needle in this situation permits free movement of the patient's joints and obviates the need for immobilization of the forearm. When a desirable vein is not present in the recommended site, the dorsal veins of the hand or the veins of the antecubital fossa may be used.

4. The skin should be properly cleansed and sterilized before needle is inserted.

5. A tourniquet should be applied above the elbow to distend the veins and facilitate venepuncture.

6. The needle is inserted into the lumen of the vein well up toward the hub, a gauze sponge placed beneath the needle hub, and the needle fixed in place with adhesive (or scotch electric tape).

7. Attach adapter of intravenous set to needle (first rid adapter of air bubbles) after removal of tourniquet, and allow solution to flow in rapidly until 10 to 15 cc. have entered. Note any swelling or infiltration about needle point; and if present, stop flow, remove needle and re-introduce in a different vein in the same or opposite forearm.

8. Refer to attached diagram and note manner in which tubing is looped on forearm and taped so that these become "a part of the forearm."

9. The rate of flow is regulated by the fine adjustment clamp so that solution enters at a speed of about 50-60 drops per minute; thus, the entire quantity of 2000 cc. will require 8-10 hours for introduction.

General Medical Care During 5-Day Intravenous Drip:- 1. Routine soap-suds enema should be given the night before treatment is begun, and whenever indicated thereafter.

2. Diet may be of the routine ward variety, except on the first day when it should be liquid.

3. Patient should receive fluids between meals, particularly of the high carbohydrate variety.

4. Patients should be confined to bed during the entire treatment course and for 3 days post-treatment.

Dosage of Bismuth with Intravenous Drip Method:- 1. A suspension of bismuth subsalicylate in oil is employed.

2. Patient should receive 0.2 gm. bismuth subsalicylate (not 0.2 gm. of bismuth metal\*) intramuscularly as soon as the diagnosis of early syphilis is

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\* 0.2 gm, bismuth subsalicylate = 0.13 gm. bismuth metal.

confirmed.

3. The second dose of 0.2 gm. should be given on the third day of treatment, the third dose of 0.2 gm. on the sixth day and a fourth dose of 0.2 gm. on the ninth day before final discharge.

#### TECHNIQUE OF 10-DAY MULTIPLE INJECTION INTENSIVE ARSENOTHERAPY FOR

#### SYPHILIS

The recommended period of days of treatment for the multiple injection system is ten. With this treatment system patients need not be confined to bed; but they must be treated in the hospital and observed for at least two days after the last injection of mapharsen. Routine ward diet may be employed.

Two injections of mapharsen are given daily over a ten day period. The injections are given in the morning and evening of each day seven to 12 hours apart (preferably 12 hours). Dosage is governed roughly by weight. Patients weighing 50 to 70 kg. (110 to 154 pounds) should receive 0.05 gm. of mapharsen twice daily for ten days. Patients weighing between 70 and 90 kg. (155 to 200 pounds) should receive 0.06 gm. of mapharsen twice daily for ten days. The dosage may be increased to 0.070 gm. in each injection for patients weighing over 90 kg. (200 pounds). Each dose of mapharsen should be dissolved in from 8 to 10 cc. of distilled water. The solution should be aerated and rapidly injected promptly after preparation. In cases where solutions are made in bulk, individual doses should be given within at least a two hour period after preparation. The intravenous route is used for injections. The needle should be inserted well into the lumen of a vein so that blood can be withdrawn freely into the syringe.

On the first, fourth, eighth and twelfth days, 0.2 gm. of bismuth subsalicylate in oil should be injected deeply into alternate gluteal muscles.

#### REACTIONS FROM 5-10 DAY INTENSIVE ARSENOTHERAPY AND THEIR MANAGEMENT

A. Minor Reactions:- 1. Pain in the arm:- cold wet dressings, ice-bag, aspirin; codeine if severe.

2. Nausea and vomiting:- give only fluids by mouth, and sedation if necessary. If persistent, discontinue treatment temporarily. may give 5% or 10% dextrose solution alone intravenously.

3. Mild headache:- aspirin or codeine usually gives prompt relief. If headache is severe, increasing and persistent, consider this as possible prodrome of toxic encephalopathy (see below).

4. Primary fever:- occurs on the first day of treatment especially with intravenous drip; if temperature goes above 101.4°F. discontinue drip for the day. Next day drip may be reinstated, practically always without

recurrence of fever. This early fever need not cause omission of the second daily dose when multiple syringe method is used.

Primary fever is usually accompanied by intensification of the syphilitic lesions (Herxheimer reaction). Symptomatic treatment may be used, if necessary.

5. Secondary fever:- Secondary rises of temperature in excess of 101° F. at any time after the first day of treatment are an indication for interrupting therapy. Mapharsen should not be given again until the temperature is normal. If fever recurs when treatment is reinstated, efforts at intensive arsenotherapy should be abandoned entirely.

Secondary fever is occasionally associated with a mild toxicoderma, but not necessarily so.

If the patient has received at least a total of 800 milligrams (0.8 gms.) of mapharsen before the appearance of fever, intensive arsenotherapy by any system should not be reinstated. In this case all further arsenical therapy may be omitted, but the patient should receive a total of at least 12 weekly intramuscular injections of bismuth subsalicylate before all treatment is stopped.

Symptomatic treatment for this reaction may be used, if necessary.

6. Toxicoderma:- usually appears in the post-treatment period, on the seventh day, and is often accompanied by fever. The type is most commonly morbilliform, scarlatiniform, or urticarial, and there is no exfoliation. This is not arsenical exfoliative dermatitis, and is not a serious sensitizing reaction. The rash usually fades in 1-1/2 to 4 days without therapy. Symptomatic treatment may be used, when indicated.

Since this reaction does not usually occur with the intravenous drip method until all treatment has been completed, it has no bearing on interruption of such treatment. When the 10-day multiple injection system is used, the occurrence of this "ninth day erythema" is an indication for interrupting treatment. This reaction may be associated (rarely) with toxic encephalopathy (see below), and continued treatment may increase this risk.

7. Renal damage:- usually insignificant, consisting of minor traces of albumin, occasional red and white blood cells. No treatment is needed.

Marked albuminuria or hematuria is a signal for discontinuing treatment.

8. Peripheral neuritis:- rarely encountered, and only in the post-treatment period. Usually manifested only by subjective symptoms, most often paraesthesias. Objective changes are rare and only sensory in type, never motor.

9. Nitritoid reaction:- rarely observed with multiple injections or with the intravenous drip procedure, unless the rate of flow of the latter is inordinately fast.

B. Major Reactions:- 1. Severe headache:- especially towards the 4th or 5th day of treatment, the occurrence of severe, persistent and increasing headache, not readily relieved by aspirin or codeine, should be viewed as of possible serious import (prodrome of toxic encephalopathy). It is best to discontinue intensive therapy and after a rest interval from all arsenical therapy of at least 4 weeks (this rest period to be occupied with weekly bismuth injections), to place the patient on the standard 26 week treatment schedule, the duration of which may be shortened to the extent of the mapharsen dosage before the reaction occurred (e.g., if the patient received a total of 400 mgm. mapharsen before the reaction, 2000mgm. additional should be given by injections twice weekly with bismuth added as in the standard schedule).

2. Jaundice:- this is an uncommon complication and calls for discontinuance of intensive arsenotherapy.

For treatment of the reaction, the patient may be given intravenous 10% dextrose solution, high carbohydrate-low fat diet, and injections of liver extract therapeutically. Intestinal elimination should be encouraged with saline cathartics.

3. Blood dyscrasias (especially purpura or bleeding from any part of the body):- rarely encountered, but necessitate permanent discontinuance of all arsenotherapy. Treatment usually consists of blood transfusions.

4. Exfoliative dermatitis:- rarely, if ever, encountered. Requires permanent discontinuance of arsenotherapy. Symptomatic treatment, dextrose solution intravenously and injections of liver extract may be used.

5. Encephalopathy:- may be manifested by severe headache, vertigo, tremor, fever, unusually severe nausea and vomiting, mental confusion, disorientation, and apathy; by single or repeated convulsive seizures, and by prolonged chorea. In serious instances hyperthermia usually supervenes and death may result. May occur on the 3rd to 5th day of treatment, or not until the 6th or 7th day, rarely thereafter. Often preceded by headache of increasing severity (see above).

In mild cases, the suspicion of toxic encephalopathy should be checked by examination of the spinal fluid for globulin or increased protein. If such tests are positive, further treatment with arsenical drugs should be abandoned. If the spinal fluid is normal, treatment may be resumed if the symptoms have completely disappeared and the temperature is normal.

Treatment of this serious reaction is of uncertain value. Suggested procedures include drainage of cerebrospinal fluid (20 to 40 cc.) in repeated taps daily; dehydration by use of intravenous 50% sucrose solution, 50 to 200 cc. Sedation is of value in all cases. Where symptoms are mild, any of the barbiturates may be used by mouth. If convulsions occur, sodium amytal 0.24 gm. (3-3/4 grains) may be given intravenously or intramuscularly (this dose may be repeated every 2-3 hours for several doses if convulsions occur or the patient is restless); or 1 to 2 cc. of paraldehyde may be slowly given intravenously. Oxygen inhalations should also be given.

N. B.-- A new, secret compound (code name Bal) may soon be available for the treatment of serious arsenical poisoning. If the compound can be obtained, it should be used according to directions to be supplied in every instance of encephalopathy, jaundice, exfoliative dermatitis, or other serious reaction.

POST-TREATMENT ROUTINE AFTER 5-10 DAY INTENSIVE ARSENOTHERAPY

(TO BE CARRIED OUT BEFORE DISCHARGE FROM HOSPITAL)

1. Complete physical examination.
2. Laboratory studies:-
  - a. STS, titered if possible.
  - b. Urine analysis (complete).
  - c. Complete blood count (hemoglobin, red blood cell and white blood cell count and differential).
  - d. Other laboratory procedures (icteric index, serum bilirubin, urobilinogen, NPN), where indicated.

OUTLINE OF PROPOSED 12-WEEK SCHEDULE OF MODIFIED INTENSIVE TREATMENT

1. Patients to be treated with mapharsen three times weekly (Monday, Wednesday and Friday; or Tuesday, Thursday and Saturday) at the following dosage scale:-

Less than 120 lbs. (55 kg.)	50 mg.
120-155 lbs. (55-70 kg.)	60 mg.
Greater than 155 lbs.	70 mg.

Treatment is to continue for 12 weeks or a total of 36 injections. Hospitalization is not necessary, and patients are to be treated on "duty status."

2. Patients to receive intramuscular injections of bismuth subsalicylate (0.2 gms., equivalent to 0.13 gms. of metallic bismuth) once weekly throughout the course of mapharsen treatment, to a total of 12 injections.

FOLLOW-UP OBSERVATION AFTER ALL METHODS OF INTENSIVE ARSENOTHERAPY

1. Patient should be re-examined at monthly intervals for a period of six months, or longer if possible.
2. Re-examination should include a complete physical examination with special attention to the mucous membranes of the mouth and throat, the genitals and the peri-anal region for easily overlooked evidences of infectious relapse.
3. An STS, preferably titered, should be performed monthly for six months, and then at the 9th and 12th months. (The STS usually becomes negative at the

12th - 16th week after the start of treatment).

4. Examination of the spinal fluid should be done, if feasible, sometime between the 6th and 12th month; the Syphilis Register should not be closed without at least one complete negative examination of the spinal fluid.

5. Patient should not receive any further antisyphilitic therapy, except as specifically set forth under "management of the unsatisfactory case."

#### MANAGEMENT OF THE UNSATISFACTORY CASE

1. A case must be considered as unsatisfactory, i.e., a treatment failure, if

a. There is definite objective evidence of infectious relapse, corroborated by a positive STS and if possible by positive darkfield examination.

b. There is incontrovertible evidence of serologic relapse without clinical relapse, i.e., the patient's STS has dropped to negative or near negative and then to persistently strongly positive (this is best interpreted by titered STS).

c. Seroresistance, i.e., where the STS has never reverted to negative but remains persistently positive (preferably determined by a constant titer of quantitative tests) for a 6 months' period after treatment.

2. A patient who has become clinically cured and serologically negative and remained so until the 12 month of observation, and in whom the spinal fluid is negative, may be discharged from observation as a "satisfactory result," and the Syphilis Register closed. Should such a person return at a later date with a new darkfield positive penile lesion, this may be considered as a ~~xxx~~ relapse ~~infection~~ and the patient may be retreated in the original manner.

3. The unsatisfactory case (infectious relapse, serologic relapse, seroresistance), and the new infection (as set forth in paragraph 2 above) may be retreated by intensive arsenotherapy at the discretion of the medical officer, except in the event of serious reaction from the original treatment.

4. The results of intensive retreatment of the unsatisfactory case have not been fully evaluated, but appear to be less satisfactory than original treatment.

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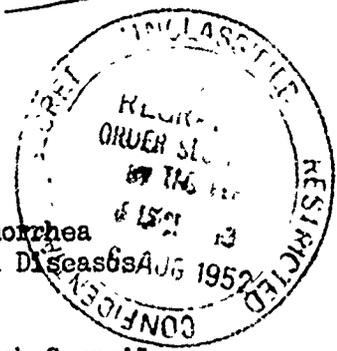
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Division of Medical Sciences  
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Office of Scientific Research and Development

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SUBCOMMITTEE ON VENEREAL DISEASES  
of the  
COMMITTEE ON MEDICINE



Minutes of a Conference on Human Experimentation in Gonorrhea  
Held under the Auspices of the Subcommittee on Venereal Diseases  
March 12, 1943.

On March 12, 1943, there was held at the National Research Council, Washington, D.C., under the auspices of the Subcommittee on Venereal Diseases, a conference on the subject of the chemical prophylaxis of gonorrhoea in human volunteers. Present were the following:-

From the Subcommittee on Venereal Diseases: Dr. J. E. Moore, Chairman, and Dr. Oscar Cox.

From the National Research Council - Committee on Medical Research:- Doctors Lewis H. Weed, A. N. Richards, E. C. Andrus, W. C. Davison, T. R. Forbes, R. G. Harrison, G. H. Guetst, and Joseph Ferrebee.

From the U. S. Army: Lt. Cols. T. B. Turner and R. G. Prentiss, Jr.; Maj. W. A. Brumfield.

From the U. S. Navy: Capt. W. W. Hall, Lt. Cndr. W. H. Schwartz, Lt. J. F. Shrouts.

From the U. S. Public Health Service: Drs. R. A. Vonderlehr and Harry Eagle.

From the Office of Scientific Research and Development: Mr. J. B. Donovan.

From the Federal Bureau of Prisons: Mr. J. B. Bennett, Director, and Dr. Marion R. King (U.S.P.H.S.)  
Investigators: Drs. C. M. Carpenter, Alfred Conn, and C. Phillip Miller.

From the New York City Health Department: Dr. E. L. Stebbins, Commissioner.

From the Royal Army Medical Corps: Lt. Col. A. J. King (London)

From the Food and Drug Administration: Dr. H. O. Calvery.

The Chairman briefly reviewed the progress of negotiations with OSRD looking toward human experimentation in the chemical prophylaxis of gonorrhoea.

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He reported that he had been directed by Dr. Vannevar Bush and Dr. A. N. Richards to investigate the feasibility of carrying out such experimentation in Federal prisons rather than in State institutions; and that accordingly he, the Chairman, had discussed the situation with Mr. James V. Bennett, Director of the Federal Bureau of Prisons. This discussion resulted in a letter from Mr. Bennett to the Chairman, as follows:-

February 26, 1943.

"Dr. J. E. Moore, Chairman  
Subcommittee on Venereal Diseases  
804 Medical Arts Building  
Baltimore, Maryland.

My dear Dr. Moore:

Following the discussion we had in this office relative to the feasibility of undertaking a proposed research project pertaining to the use of Federal prisoners on a voluntary basis as subjects in a study of prevention, mode of infection, and cure of gonorrhoea, I discussed the plan with the Attorney General.

The Department is sympathetic toward the project, especially since it is understood that studies of this nature will be of great help in promoting the effectiveness of the armed services. We shall, therefore, be glad to discuss the feasibility of this project with you or your committee further on the understanding that we do not feel we should, in securing volunteers, indicate that commutation of sentence or a pardon for any Federal prisoner will be given as a reward for participating in the project. We cannot obligate the Government in any manner insofar as reduction of sentence for those who volunteer is concerned. It is believed, however, that the U. S. Board of Parole would be willing to give each subject who participates in the project due credit and consideration for his willingness to serve his country in this manner when he becomes eligible for parole consideration in the usual manner.

It is also my understanding that it will be possible to grant each prisoner who participates in the project some monetary consideration to compensate him for loss of his earning capacity while engaged on the project. My understanding is that granting each subject an amount of approximately \$100 and providing him with adequate insurance for any possible permanent disability are also feasible.

I think, too, that in order to protect the general morale of the several institutions, it would be well to carry out the study on a strictly secret and military basis for at least the time being.

I have been governed in my favorable representation of the plan to the Attorney General by the fact that the project seems genuinely promising to the Surgeons General of the Army, Navy, and Public Health Ser-

"vice. I am advised that the technical aspects of the problem do not appear too difficult and that the major problem appears to involve administrative matters relating to the selection of the subjects and the organization of the staff. It might be, therefore, that we shall need to call upon the OSRD for supplementary personnel to assist us in this matter.

I should be very glad to discuss the whole matter with your committee further if you think the project should be undertaken in view of the principles I have outlined as governing our part in the program.

With kind personal regards,

Sincerely yours,

S/ James V. Bennett, Director,  
Federal Bureau of Prisons "

The Chairman then brought to the attention of the conference the memorandum of a conversation of March 5, 1943, between himself and Dr. A. N. Richards, the most important point of which was that Dr. Bush desired that, if possible, "arrangements for these experiments should be made between the Office of Scientific Research and Development and the Department of Justice rather than with universities," and suggested that the Public Health Service assume responsibility for the entire investigation. This memorandum led to further correspondence between the Chairman and Dr. Thomas Parran, as follows:-

"Surgeon General Thomas Parran  
U. S. Public Health Service  
Bethesda Station, Md.

March 8, 1943.

Through Assistant Surgeon General R. A. Vanderlehr

Sir:

After detailed diplomatic negotiations with many governmental agencies, the proposals for a contract for human experimentation in the chemical prophylaxis of gonorrhoea have been approved in principle by Dr. Vannevar Bush, Director of the Office of Scientific Research and Development. In conversation with Dr. Richards, Chairman, Committee on Medical Research, Dr. Bush had expressed the wish that the arrangements for these experiments which, incidentally, are probably to be limited to inmates of Federal prisons, should be made directly between OSRD and the Department of Justice rather than with universities as contracting agencies. When Dr. Richards mentioned this point to me, I made the suggestion that perhaps it would be possible for OSRD to make the arrangements for the carrying out of these experiments directly with the U. S. Public Health Service, since this is the agency responsible for the medical care of inmates of Federal prisons.

Preliminary conversations with Dr. Vanderlehr had indicated the probable impossibility of assigning to these studies officers already con-

missioned in the U. S. Public Health Service, for the double reason that it might be difficult to obtain medical and bacteriologic personnel sufficiently experienced, or if such persons were already available, it might be difficult to detach them from their present assignments to such studies. I then suggested to Dr. Richards that perhaps the Public Health Service might be willing temporarily to commission certain physicians drawn from the responsible investigators who have made proposals for contract, or from their staffs, and to employ on a temporary excepted Civil Service status the necessary technical assistance. Dr. Richards replied that if this could be done the funds wherewith to finance it would probably be transferred from OSRD to the Public Health Service direct.

Yesterday, Sunday March 7, I discussed this matter briefly over the telephone with Dr. Parran whose initial reaction was unfavorable. It is believed, however, that this suggestion will come up for further discussion at a conference which, in view of Dr. Bush's approval in principle of the experiment, will be arranged at the National Research Council at 10:00 A.M. on Friday, March 19. The purpose of this conference will be to draw up the exact outlines of the experiment, both from administrative and medical points of view, and to determine as accurately as possible its cost. The conference will include representatives of the Committee on Medical Research, the U. S. Army, Navy, and Public Health Service, the Federal Bureau of Prisons, the Subcommittee on Venereal Diseases, National Research Council, and the original proposers of contracts, Dr. C. Phillip Miller, University of Chicago, Dr. C. M. Carpenter, University of Rochester, and Dr. Alfred Cohn, New York City Health Department. Both Dr. Parran and Dr. Vonderlehr will receive formal invitations to this conference from Dr. Wood, Chairman of the Division of Medical Sciences, National Research Council. It is earnestly hoped that both Dr. Parran and Dr. Vonderlehr will be able to attend, and that the suggestion for taking over the experiment by the Public Health Service, perhaps in the manner briefly outlined above, may be further explored.

Respectfully,

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

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UNITED STATES  
PUBLIC HEALTH SERVICE

Washington

March 11, 1943

"Dear Doctor Moore:

Reference is made to your letter of March 8 concerning the forthcoming conference at the National Research Council on March 19th.

" I have attempted to state the position of the Public Health Service in respect to administration of the proposed studies in a memorandum to Dr. R. A. Vanderlehr, which is attached."

Sincerely yours,

S/ Thomas Parran  
Surgeon General

March 11, 1943

MEMORANDUM

To: Dr. R. A. Vanderlehr  
From: Dr. Thomas Parran

Subject: Letter of March 8 from Dr. J. E. Moore

It is the general policy of the Public Health Service not to seek funds from the Committee on Medical Research OSRD for the support of research activities of the Public Health Service. Minor exceptions may have been made to the general rule but in a number of discussions with the Bureau of the Budget the general policy stated has been agreed upon.

If it is necessary for the Public Health Service to undertake added research activities related to the war, either on its own initiative or on request of the Army or Navy, supplemental or deficiency appropriations are requested, -if such studies cannot be carried out with available funds.

In view of the substantial funds being expended by your division for research in the venereal diseases, we would not be justified in asking for a grant for the proposed studies from the OSRD.

It would seem more desirable for the OSRD to enter into a contract with the Department of Justice. Dr. Moore's statement is not technically correct when he says that the Public Health Service "is the agency responsible for the medical care of inmates of Federal Prisons." Medical officers of the Public Health Service are assigned for duty with the Bureau of Prisons, are administratively under the jurisdiction and control of that Bureau and the cost of their salaries is paid by reimbursement of Public Health Service funds. The Public Health Service continues to have the responsibility only for the professional competence of the personnel and the standards of professional care in the prisons."

A general discussion ensued.

Mr. Bennett, Director of the Federal Bureau of Prisons, stated that from the standpoint of his Bureau it would be particularly desirable to concentrate all of this experimentation at one institution in Terre Haute, Indiana, to which

volunteers obtained from other institutions could be temporarily transferred for the duration of the experiment. The travel expense involved in this transfer would be borne by the Federal Bureau of Prisons. It was agreed that the preliminary screening of volunteers from both administrative and medical standpoints would be carried out by the Federal Bureau of Prisons; that acceptable volunteers should fall within the age group 21 to 45; and that excluded from the experiment should be those prisoners eligible for parole within six months, those serving very long terms, and certain serious offenders, and those suffering from serious disease, physical or mental, including homosexuals.

The question was discussed of reward to volunteers. Mr. Bennett felt that a cash credit, probably of \$100. per volunteer, should be given, in part to stimulate volunteers, and in part actually to compensate the volunteer for loss of income for time spent away from work. Mr. Bennett further stated that the Federal Bureau of Prisons was prepared to restore for volunteers' lost "good time", i.e., a prisoner whose behavior is excellent throughout the period of his incarceration, is discharged at the expiration of two-thirds of his sentence. Infractions of prison discipline, however, are punished by a loss of this "good time", and repeated infractions may result in the loss of all of it, requiring a prisoner to serve out the entire sentence imposed by the Court. It is this lost "good time" which will be restored to volunteers. In addition, volunteers will be favorably recommended to the Federal Parole Board.

Mr. Bennett pointed out that the cooperation of the responsible investigator in obtaining and screening volunteers at the several Federal institutions will be essential. The appeal to prisoners to volunteer will be made promptly by the responsible investigator or his representative, and by the officials of the Federal Bureau of Prisons, including particularly the wardens and the medical officers of the U. S. Public Health Service assigned to these prisons. As a result of this phase of the discussion it was decided that a team would be necessary, composed of a full time physician, a full time bacteriologist, and a clerk, to travel among the various Federal institutions to cooperate with the Federal Bureau of Prisons in the obtaining and medical screening of volunteers who, after selection at the several Federal institutions, will then be transferred to Terre Haute for the final experiment. It was agreed that from the standpoint of the responsible investigator this preliminary screening should follow the procedure outlined in Section I, of Exhibit "B" of the "Proposed Plan of Procedure" in the study of chemical prophylaxis among human volunteers among prison inmates, which was appended to the Minutes of the December 29, 1942, Conference on Human Experimentation, held under the auspices of the Subcommittee on Venereal Diseases. One amendment was made in this outline of procedure, this amendment being in paragraph 13c, which was amended to read as follows:-

"That at least two negative cultures of urine sediment obtained by voiding after massage of the urethra and prostate, these cultures to be obtained at three-day intervals."

The question was raised as to the availability of fever therapy in the event

of sulfonamide resistant subjects. Dr. King reported that fever cabinets were available at the Federal prison at Springfield and, if necessary, one of those cabinets could be moved to Terre Haute.

The discussion then turned on the manner in which the experiments were to be carried out, in view of Dr. Bush's wish that the entire experiment be handled, if possible, through the U. S. Public Health Service. Dr. Vonderlehr reported that this was entirely feasible; that the Public Health Service was prepared to devote from \$50,000 to \$75,000 of its own funds to this purpose. He also reported that personnel drawn from the regular Corps of the U. S. Public Health Service was not available, since all of those with adequate training were all engaged on equally important work. He stated, however, that it would be possible for the U.S. Public Health Service to appoint responsible investigators as consultants to the U. S. Public Health Service and to commission with temporary rank one or more full time medical officers for the actual prosecution of this work. It would also be possible with Public Health Service funds to employ on a temporary accepted Civil Service status bacteriologists and clerks.

This arrangement appears temporarily to remove the necessity for OSRD funds on contracts. There remains the possibility that if the funds at the disposal of the Public Health Service are not adequate for the completion of the experiment, particularly with respect to compensation of volunteers, OSRD funds may be obtained for this purpose, and this question will be subsequently raised if necessary.

In view of the willingness of the Public Health Service to assume responsibility for the entire experiment, the relationship to the experiment of those physicians who have already made application for OSRD contract for this purpose, namely Doctors Miller, Carpenter, and Cohn, is somewhat altered by virtue of the geographical necessities of the situation. It seems desirable that the work at Terre Haute be carefully supervised from clinical and bacteriologic standpoints by competent persons who can make frequent visits to the institutions. These investigators most closely geographically situated to Terre Haute are Drs. C. Phillip Miller and Russell Herrold, both of Chicago. Dr. Miller felt that it would be possible for him to go to Terre Haute for one or two days a week, and Dr. Herrold, who was not present at the meeting but who was communicated with by long distance telephone, also expressed his willingness to serve as a consultant as often as once weekly, if necessary.

In order to retain the cooperation of those previously interested in the problem and to broaden the scientific responsibility for the work, Dr. Vonderlehr suggested and the conference agreed that an Advisory Committee to the Public Health Service be appointed, composed of J. E. Moore as Chairman, and the following physicians: Dr. C. Phillip Miller, Dr. Russell Herrold, Dr. Oscar Cox, Dr. C. M. Carpenter, and Dr. Harry Eagle. Suggestions were then made for young physicians who might be given temporary commissions in the Public Health Service for the actual carrying out of the detailed work. Dr. William G. Beadenkopf, now resident physician in Medicine at the University of Chicago, is immediately available. It was agreed that Dr. Vonderlehr would forward to Dr. Miller the application blanks for Dr. Beadenkopf to apply for a temporary commission which can probably be arranged

within the next two weeks. It was further agreed that, as soon as commissioned, Dr. Beadenkopf would be ordered to active duty and, pending the organization of the experiment at Terre Haute, would be stationed for clinical experience in the clinics of Doctors Russell Herrold or Oscar Cox, or both. It was then tentatively agreed that Dr. Beadenkopf would be assigned to the experiment at Terre Haute.

In view of the necessity for medical screening of volunteers at institutions other than Terre Haute, it was also agreed that a second full time physician would be desirable. For this position was suggested the name of Dr. Robert Westphal, now employed in the New York State Department of Health. Dr. Westphal is an M.P.H. from the Johns Hopkins School of Hygiene, has had prison experience in New York State, and has had two years' experience in the field of gonorrhea. Dr. Vanderlehr agreed to approach Dr. E. S. Godfrey, Commissioner of Health of New York State, to ask for the temporary loan of Dr. Westphal to this project. If Dr. Godfrey is willing to release Dr. Westphal, Dr. Moore is to approach him with the definite offer of the position.

In the event of the unavailability of Dr. Westphal, Dr. Carpenter suggested the name of Dr. John Weaver, now employed in the Glynn County Georgia Health Department. Should neither Dr. Westphal nor Dr. Weaver be available, Drs. Moore and Engle agreed to survey the names of persons who have completed the M.P.H. course in venereal disease control at the Johns Hopkins School of Hygiene to see if other suitable candidates could be obtained therefrom.

As to bacteriologic technicians it was agreed that among the several persons present Drs. Carpenter, Cox, Miller, and Moore would survey the possibilities of releasing two technicians from their own laboratories or of obtaining additional technicians who might be trained in Dr. Miller's laboratory.

It was finally agreed that the tentative set up would consist of a team at Terre Haute to be composed of Dr. Beadenkopf, a bacteriologist, and a clerk; and that the itinerant team to travel among Federal institutions for the selection and screening of volunteers would likewise consist of a physician, if possible Dr. Westphal, a bacteriologist, and a clerk.

It was agreed that it would be desirable at the outset of the actual inoculation experiments in Terre Haute for a senior consultant to be in residence for a minimum of 10 to 14 days in order to get the experiment well started. Either Dr. Cox or Dr. Carpenter could go to Terre Haute for this purpose, as also could probably Dr. Miller.

It was finally agreed that at the earliest possible moment and as soon as the two resident physicians could be definitely secured, a conference would be held in Terre Haute under the joint auspices of the Public Health Service and the Federal Bureau of Prisons to which would be invited the Advisory Committee to the Public Health Service named above, the two resident physicians, Drs. Vanderlehr and King of the Public Health Service, and representatives of the U. S. Army and Navy. This conference will arrange the final practical details of the work.

At various points during the general conversations there was held a prolonged discussion of insurance. Dr. Vanderlehr reported that the Public Health Service could probably not obtain liability insurance for itself or for the persons actually engaged in performing the experiments. Dr. Richards agreed to explore further with OSRD other avenues through which such insurance might be obtained. The question also arose of insurance for the volunteers and Dr. Moore was directed to consult with Lloyds of London and with the U. S. Veterans' Administration in order to determine if such insurance could be obtained.

Finally there ensued a discussion as to the type of experiments to be undertaken. Since the memoranda of December 29 were prepared, it appears less desirable to investigate the prophylactic effect of the oral sulfonamides than was then the case; and more desirable to investigate the efficacy of local prophylactic agents. It was brought out that the most promising single agent was at the moment an arsenical drug. Dr. Eagle reported on the studies so far available on such arsenical drugs to the effect that a representative amide-substituted arsenoxide in a concentration of 1:500 in propylene glycol will prevent syphilis in experimental animals locally applied four hours after inoculation; that this particular product had a moderately good in vitro gonococidal activity, and that its activity against the virus of lymphogranuloma, while under study, is not as yet definitely known. So far there is apparently no correlation among arsenicals between spirocheticidal, gonococidal, and viricidal activity. Dr. Eagle also reported that at the moment a phenoxo-acetamide derivative has apparently the best over-all activity against these three infections, and that ultimately it may prove to be the drug of choice. Unfortunately, preliminary experiments indicate that an arsenical drug has no activity against chancroid.

Dr. Eagle also reported that further work carried out by himself and by Dr. Carpenter had shown that certain penetrants possess both spirocheticidal and gonococidal activity, but that unfortunately Dr. Calvery had determined that those with the greatest activity in these two respects were also the most toxic locally.

In summary of the work at present available, Dr. Eagle stated that the preparation for ultimate clinical trial should probably be a stable arsenical drug in an esthetically pleasing ointment base which will not reduce its activity, with or without a sulfonamide (if arsenic proves to be of no value against chancroid) and with or without a detergent, depending on the over-all activity of the detergent itself or the action of the detergent in promoting or decreasing the activity of the drugs. In view of the work in progress by many other investigators, along these several lines, it was also indicated that it would probably be five or six months before such final preparation would be available for clinical trial.

In spite of this, however, and to aid in the development of such a final preparation, it was agreed that human experimentation should begin immediately along three lines:-

- First, to determine the prophylactic activity of a sulfonamide ointment;
- Second, to determine the prophylactic activity of an arsenical ointment (studies on the local toxicity of which are now under way);

Third, to determine the prophylactic activity of a representative detergent.

When these three studies have been completed in man, together with the simultaneous laboratory investigations now under way on all of them, it will be possible to develop the fourth and final experiment, in which the combination of these several factors can be studied.

An estimate was made of the total number of volunteers, considering the necessity for preliminary study of the minimal infective dose. It was felt that probably a total of 250 - 300 volunteers would be essential.

At 5:00 P.M. the conference adjourned.

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RESUMÉ

MINUTES OF A CONFERENCE ON BIOLOGIC FALSE POSITIVE  
SEROLOGIC TESTS FOR SYPHILIS  
Held under the auspices of  
the  
SUBCOMMITTEE ON VENEREAL DISEASES- NATIONAL RESEARCH COUNCIL  
in  
Washington, D.C. January 26, 1943.

Present:

From the Subcommittee on Venereal Diseases, Dr. J. E. Moore, Chairman,  
and Dr. J. F. Mahoney;  
From the U. S. Public Health Service, Dr. Harry Eagle;  
The following OSRD contract holders: Doctors Dan Moore, Columbia  
University, Elvin A. Kabat, Columbia University, Bernard Davis,  
Neurological Institute, Doctors Hans Neurath and Joseph W.  
Beard, Duke University; and Dr. Herbert Lund, Cleveland City Hosp.  
The following interested persons: Major Charles Rein, U. S. Army,  
Mr. Ad Harris, Venereal Disease Research Laboratory, Stapleton,  
N.Y., Dr. W. C. Davison, National Research Council

Report by Major Rein:

Of 100 patients inoculated with vaccinia, 35 per cent were found to give biologic false positive tests for syphilis. Most of the false results fell into the doubtful category, the highest titer observed being a serum titer of 4 (16 Kahn units). Without exception, the tests became positive within 12 to 15 days after inoculation, and the time required for eventual reversal to negative depended on the height of the false reactivity. The Wassermann in this group was the least affected of the six tests used (Kline diagnostic, Kline exclusion, Kolmer flocculation, Kolmer Wassermann, Mazzini, and Boerner); and the Mazzini and Kline exclusion tests gave the highest incidence of false reactions.

Of 50 cases of virus pneumonia, 25 per cent gave a false positive or doubtful test for syphilis, most frequently in the doubtful category. As in the case of vaccinia, these false reactions appeared 12 to 14 days after the onset, and were accompanied by a reversal in the A/G ratio. The virus complement fixation reaction was also positive in every case giving a false positive test for syphilis.

Of 85 patients with Weil's disease, 45 per cent gave false positive tests for syphilis.

Major Rein also made a preliminary report on a method which may possibly permit the differentiation of syphilitic sera from those giving biologic false positive reactions. That method is based on the observation that syphilitic sera which give a negative flocculation test, if tested as fresh unheated serum, gradually become positive on aging. Moreover, if fresh human serum is added to syphilitic sera previously "activated" by heating at 56° for ten minutes, the flocculation tests again become negative. This inhibition apparently does not affect the reactivity of sera giving biologic false positive tests. In the actual procedure, 0.3 c.c. of the serum in question are added 0.15 c.c. of (a) fresh normal serum, and (b) heated normal serum. Syphilitic sera give a negative reaction in tube "A" and a positive

reaction in tube "b"; while biologic false positive sera react positively in both.

Report of Doctor Beard (Electrophoretic Studies):-

Syphilitic sera contain on the average smaller amounts of the alpha globulin and albumin fractions, more of the gamma globulin fraction, and give a lower A/G ratio than do normal sera. Antisyphilitic treatment had no demonstrable effect on these serum changes. Sera giving biologic false positive tests were intermediate between syphilitic and normal sera with respect to changes in the electrophoretic pattern. Finally, in cases of known syphilis there was no correlation between the amount of gamma globulin in the serum and the titer of the serologic test for syphilis (Wassermann, Kahn, Kline).

Report of Doctor Neurath:

Doctor Neurath has found that syphilis reagin is precipitated by 1.9 molar ammonium sulfate at 4°. In one of two sera presumably giving biologic false positive tests for syphilis, all the reactive material was precipitated at 1.3 molar concentration. Further work will be necessary to establish whether this is a regular phenomenon, permitting differentiation.

Report of Doctor Davis:

On electrophoretic fractionation of syphilitic serum the serologically most active fraction of the serum protein was found to lie between the beta and gamma globulin fractions, with some slight activity in the beta, and with the "slow" gamma fraction more active than the "fast" gamma. The gamma globulin was more anti-complementary than the other fractions, and that anticomplementary activity was inhibited by the addition of beta globulin or albumin. In the ultracentrifuge the reagin, in solutions of gamma globulin or of whole serum, sedimented faster than the rest of the serum protein, suggesting a molecular weight, perhaps as high as 900,000. Per unit solid, euglobulin contained more reagin than pseudoglobulin.

Report of Doctor Lund:-

The serum of normal, and presumably nonsyphilitic, Negroes contains larger amounts of a normal reagin-like factor than does the serum of white individuals; but even in the latter group approximately 50 per cent of the sera tested gave positive tests in high serum:antigen ratios, using Kline exclusion antigen.

Outline of Future Work

The consensus of those present was that:

(1) It must be demonstrated that the Lund technic actually demonstrates a reagin-like factor affecting all the antigens used in flocculation tests for syphilis, and not a factor which uniquely flocculates Kline exclusion antigen. In the former case, Dr. Lund's observations are of obvious significance with respect to biologic false positive tests for syphilis; in the latter case they reflect only

on the diagnostic utility of the Kline exclusion test.

(2) The studies previously carried out on syphilitic serum in the laboratories of Duke and Columbia should now be extended to include sera giving biologic false positive tests for syphilis. Since most of these sera contain small amounts of reagin, Lund's technic will necessarily have to be used for the titration of the fractions obtained. For the time being, Kline exclusion antigen will be used for those titrations; but it is understood that simultaneously an attempt will be made to develop this same technic with other antigens.

(3) Doctor Mahoney's laboratory will apply the Lund technic to the protein fractions obtained by the group at Columbia. The fractions obtained by the group at Duke will probably be sent to Doctor Lund for titration, unless that technic can be developed at the Duke laboratories. Doctor Beard will investigate the latter possibility.

(4) Doctor Moore and Doctor Eagle will arrange to have a group of patients giving presumably biologic false positive tests for syphilis bled on one day for 400 - 500 c.c. The serum will be centrifuged the following day, and messengers from Duke and Columbia will pick up that serum at the Johns Hopkins Hospital and transport it immediately to the respective laboratories. A small amount of each serum will be sent to Major Rein for study by his procedure.

(5) Until those sera are made available, fractions of normal serum protein will be titrated for reagin content by the Lund procedure. If possible, those fractions should be supplied in somewhat more concentrated solution than they occur in normal serum.

~~CONFIDENTIAL~~

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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 MEDICINE

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Minutes of a Conference on the Chemical and Chemotherapeutic  
Prophylaxis of Venereal Disease  
Held at Rochester, New York, January 20 - 21, 1943.

Present at the Conference were the following persons:-

Chairman, Dr. J. E. Moore, Chairman Subcommittee on Venereal Diseases.

From the Subcommittee on Venereal Diseases, Doctors John H. Stokes, Oscar Cox, Russell Herrold, and John F. Mahoney.

The following OSRD contract holders: Dr. Herbert O. Calvery, Food and Drug Administration, Dr. Charles M. Carpenter, University of Rochester, Dr. Frank C. Combes and Dr. Orlando Canizares, New York University, Dr. Harry Eagle, U.S. Public Health Service and Johns Hopkins University, Dr. Robert B. Greenblatt, University of Georgia, Dr. Justina H. Hill, Johns Hopkins University, Dr. G. W. Rake, Squibb Institute for Medical Research, Dr. Marvin R. Thompson, Warner Institute, Dr. Stafford L. Warren, University of Rochester. Dr. Alfred Cohn of the New York City Health Department was unable to attend because of illness, but submitted his written report which appears hereafter.

From the U. S. Army, Major Robert Dyar (MC), U.S.A.A.F.

From the U.S. Navy, Lieut. J. F. Shrouts (MC), Bureau of Medicine and Surgery, and Lieut. Comdr. A. J. Pereyra (MC), stationed at the U.S. Marine Hospital, Stapleton, New York.

From the U.S. Public Health Service, Dr. R. C. Arnold, Venereal Disease Research Laboratory, Stapleton, Dr. Austin Deibert, U.S. Public Health Service Venereal Disease Center, Hot Springs, Ark.

From the Canadian Army, Capt. Donald H. Williams, Canadian Army Medical College, Ottawa.

From the University of Rochester, Doctors Helen Ackerman, George P. Berry, Ruth A. Boak, and Herbert E. Stokinger.

The following interested persons and potential OSRD contract holders: Dr. William L. Fleming, University of North Carolina School of Public Health, Chapel Hill, Dr. C. Phillip Miller, University of Chicago, Dr. A. L. Tatum, University of Wisconsin.

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Representing pharmaceutical houses cooperating with the Subcommittee on Venereal Diseases, Dr. F. V. Sander, Ortho Products Co. New Brunswick, N.J., and Dr. L. A. Sweet, Parke Davis & Company, Detroit.

From the Committee on Medical Research, Dr. George M. Guest.

After an introductory statement by the Chairman there followed a presentation of the results accomplished to date by the several OSRD contract holders in the field of chemical and chemotherapeutic prophylaxis. These follow herewith in the order presented.

HARRY EAGLE

THE PROPHYLACTIC EFFICACY OF CALOMEL OINTMENT IN EXPERIMENTAL SYPHILIS

1. Toxicity (cf. Table enclosed). Calomel ointment (USP) applied by inunction over an area approximately 4 to 5 inches square, was approximately one-fifth as toxic as the same ointment injected intramuscularly. This suggests that, under the conditions of the experiment, approximately twenty per cent of the ointment was absorbed. This result will be verified by studies of actual mercury excretion in urine and stool (Dr. Calvery).

2. Prophylactic Efficacy after Intracutaneous Inoculation (cf. Table).

Rabbits were inoculated by the intracutaneous injection of 0.1 cc. of a suspension of *S. pallida* containing  $10^7$  organisms cc. One hour later, an area approximately 4 to 5 inches square, immediately over and around the inoculated area, was rubbed for 5 minutes with varying amounts of calomel ointment as indicated in the Table. Other rabbits, similarly inoculated, were given calomel ointment on the opposite side of the back as a test of systemic efficacy. Although there was an indication that the ointment was somewhat more effective when applied over the inoculated area, the differences were slight, and may have been within the limits of experimental error. By interpolation, approximately 30 to 40 mg. per kg. of HgCL were required to prevent infection in fifty per cent of the animals; and the dosage used in man (4 gms. of a 33 per cent ointment, or 1.3 gms. of HgCL, or approximately 20 to 25 mg. per kg. in a man weighing 60 kg.), had a definite prophylactic effect, preventing infection in approximately 30 per cent of the cases.

The method of inoculation used in the above experiment is obviously a rigorous test of any prophylactic agent. The experiment described in the following paragraph, using a somewhat more subtle method of inoculation, approximates more closely the conditions which obtain in the human infection.

Although lymph node transfers have been performed in all surviving animals apparently protected by calomel, these transfers (6 months after the original experiment) were usually negative. In the series of 30 animals so studied, only 2 which failed to develop a chancre, were found to have had a symptomless infection; and one of those was an untreated control. The failure of the rabbit to develop a chancre may thus prove to be a valid criterion of successful prophylaxis.

3. The Prophylactic Efficacy of Calomel applied by Inunction Into a Superficial Cut, Inoculated with Spirochete Pallida.

Rabbits were inoculated by gently massaging (3 minutes) a suspension containing  $10^7$  organisms per cc. into a superficial incision 1 cm. long on the skin of the rabbit's back. At varying intervals after that inoculation, calomel ointment (USP) was applied in varying amounts over an area approximately 2 inches square immediately over and around the inoculated area. In a second group of animals, the ointment was given on the opposite side of the back as a control of systemic efficacy. As shown in the Table, with this method of inoculation, which approximates more closely the human infection than does the intracutaneous inoculation discussed in the previous paragraph, calomel was far more effective. Twenty-five mg. per kg., the approximate dosage now used in human prophylaxis, prevented the infection in 29 out of 30 rabbits. Moreover, this protective action of calomel was apparent even if

applied 4 hours after inoculation, and as little as 10 mg. per kg. had a definite effect. On the other hand, when the animals were given calomel by inunction on the opposite side of the back, less than half the animals were protected by 25 mg. per kg. In this experiment, unlike that described in its preceding paragraph, the results have not as yet been checked by lymph node transfers.

4. Further study:- Contrary to original expectations, calomel in the dosage used in man has proved surprisingly effective when given prophylactically in rabbits by the method described above. Under such circumstances, we must retain calomel as the basis of our prophylaxis against syphilis, at least until such time as a more efficient agent or an esthetically more pleasing preparation has been developed. Although the possible prophylaxis of syphilis with arsenicals holds promise, attempts should be made to increase the efficacy and to improve the esthetic properties of calomel ointment, should the arsenicals prove to be ineffective, excessively toxic, or both. To save time, these studies should be carried out concurrently with these on the arsenicals. The following lines of attack are suggested:

- 1) The effect of the particle size of calomel on its prophylactic efficacy. It is conceivable that smaller particles may prove more effective.
- 2) The effect of the ointment base on the prophylactic efficacy of calomel. Previous studies have been limited to the USP petrolatum-lanolin base. It is possible that a more complex oil-in-water, or water-in-oil emulsion might prove more effective.
- 3) The addition of wetting agents may favorably affect penetration and thus the efficacy of calomel ointment.
- 4) Ointment bases may be developed which may permit the incorporation of calomel in a vanishing cream, esthetically more pleasing than present preparations.
- 5) Since it is possible that ultimately we may have to use a mixture of several pharmaceutical agents, e.g., calomel and a sulfonamide, the effect of the sulfonamides as a group on the prophylactic efficacy of calomel should be investigated.

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Chairman's Comment:- Discussion brought out the fact that for the first time, this study defines the efficacy of calomel ointment in relation to dosage/body weight. The results are such as to indicate that the further studies outlined for calomel are essential in the event that the experiments on arsenical prophylaxis do not pan out as well as preliminary studies suggest.

## THE TOXICITY OF CALOMEL OINTMENT

Given by Inunction <sup>1</sup> into skin of back						Given Intramuscularly <sup>2</sup>					
HgCl <sub>2</sub> , mg./kg.	Dead <sup>3</sup>	Survived	Results recalculated after Reed and Muench			HgCl <sub>2</sub> , mg./kg.	Dead	Survived	Results recalculated after Reed and Muench		
			Dead	Survived	% dead				Dead	Survived	% dead
250	9	11	18	11	62	250	10	0	33	0	100
						160	4	2	23	2	92
						80	3	2	19	4	83
50	4	6	9	17	35	50	5	5	16	9	64
						40	1	4	11	13	46
25	3	33	5	50	9	25	3	5	10	18	36
						20	3	4	7	22	24
10	1	29	1	79	1	10	3	7	4	29	12
2	1	19	1	98	1	2	1	9	1	38	3

<sup>1</sup>Over area of approximately 20 sq. in.; rubbing time 5 minutes; 30% ointment used for large doses, 1% for small doses, both in a lanolin-petrolatum base.

<sup>2</sup>Suspension in olive oil.

<sup>3</sup>Died within 2 months. Most of toxic deaths occurred within first month; and those dying more than 60 days after treatment were arbitrarily considered adventitious deaths.

THE PROPHYLACTIC EFFICACY OF CALOMEL OINTMENT

(Administered one hour after inoculation unless otherwise indicated)

Dosage HgCl <sub>2</sub> , mg./Kg.	Given by inunction <sup>3</sup> over inoculated area <sup>1</sup>			Given by inunction, but no over inoculated area <sup>2</sup>		Given by intra- muscular <sup>3</sup> injection <sup>3</sup>	
	After intracutan- eous inoculation	After scratch inoculation	Protected Syphilitic	Protected Syphilitic	Protected Syphilitic	Protected Syphilitic	Protected Syphilitic
250	6	0			4	1	
50	7	1					5 0
25			5: 8	0	5: 5	3	
			60: 13	1	240: 4		
			240: 8	0			
10	1	8	5: 4	2	0	10	7 0
			240: 1	3			
2	0	8			2	8	1 8

<sup>1</sup>Over area of approximately 20 sq. in.; rubbing time 5 minutes; 30% ointment used for large doses, 1% for small doses, both in a lanolin-petrolatum base.

<sup>2</sup>By this method of treatment, no significant difference between animals inoculated intracutaneously or into superficial scratch; and these 2 groups not distinguished in this section of table.

<sup>3</sup>Suspension in olive oil.

Prophylactic activity of Calomel Ointment Administered 1 hour After Intracutaneous Inoculation with  $10^6$  Sp. Pallida

mg./kg/Over HgCL	Inoculated Area, by Inunction			Calomel Ointment Given:			In Skin on Opposite Side. By Intramuscular In- jection, Right Leg		
	Dead <sup>1</sup>	Protected <sup>2</sup>	Syphilitic <sup>3</sup>	Dead	Protected	Syphilitic	Dead	Protected	Syph.
250	4	6 (6)	0	5	4 (2)	1	10	0	0
50	2	7 (6)	1*	2	5 (5)	3	5	5	0
10	1	1 (1)	8	9	0	10	3	7 (5)	0
2	1	0	8	0	2 (2)	8	1	1 (1)	8

20 CONTROLS (NO CALOMEL): 3 deaths, 15 chancres, 1 symptomless infection\*, 1 non-syphilitic.

<sup>1</sup>Died within first 2 months after inoculation.

<sup>2</sup>No chancre formation. The numbers in parenthesis represent the number of rabbits giving negative lymph node transfers 6 months after inoculation.

<sup>3</sup>Typical darkfield-positive lesion at site of inoculation. The asterisks represent 2 animals who failed to develop chancre, but did have a symptomless infection as administered by positive lymph node transfers 6 months after inoculation.

HARRY EAGLE

THE PROPHYLACTIC EFFICACY OF ARSENICALS

Over the past six years, a large series of substituted phenylarsine oxides have been studied with respect to their treponemicidal activity in vitro and toxicity in white mice. A large number of these have further been studied with respect to their toxicity in therapeutic efficacy in the treatment of rabbit syphilis.

We have previously found that strongly acidic substituent groups introduced into phenylarsine oxide regularly caused a striking decrease in direct treponemicidal activity against *T. pallidum*, without a commensurate decrease in toxicity. The potential therapeutic utility of these compounds was therefore even less than that of the simple unsubstituted phenylarsine oxide. However, when the acidic group was blocked, as in ethyl or methyl esters, or as in the sulfone and phenone compounds, the treponemicidal activity was largely restored, and the ratio of treponemicidal activity: toxicity was increased as much as fourteen-fold, in several cases significantly exceeding that of the parent compound.

In the light of that finding, a series of phenylarsine oxides was prepared in which an acidic substituent group had been blocked by amide formation. The majority of these amides have proved to be actively treponemicidal and relatively low in toxicity (1st section of Table ). The ratio of treponemicidal activity: toxicity, which may be taken as a rough measure of potential therapeutic utility, was usually 2 to 6 times as favorable as that of the parent phenylarsine oxide, due primarily to the uniformly low toxicity of these compounds. Some of these compounds have shown a chemotherapeutic index in the treatment of rabbit syphilis equal to or exceeding that of mapharsen, and on that basis are of potential value in the treatment and prophylaxis of syphilis. The favorable effect of amide-substituted has been so regular as to suggest that further study may disclose other related compounds of greater therapeutic utility than any of those here described.

The favorable effect of amide substituents on the toxicity of phenylarsine oxide was observed whether that amide group was attached directly to the benzene ring, as in the case of 3- and 4-CONH<sub>2</sub> and -SO<sub>2</sub>NH<sub>2</sub> compounds, or through some intermediate linkages. Moreover, the integrity of the amide group was usually essential for the favorable activity: toxicity ratio. When either or both of the amide hydrogens were substituted, the compound usually developed properties apparently determined by the new terminal substituent. Although treponemicidal activity was usually increased by such substitution, toxicity was increased to an even greater degree, giving a less favorable ratio. In this group of compounds, the activity and toxicity of the compound had thus reverted toward that of the simple unsubstituted phenylarsine oxide, or of phenylarsine oxides with such indifferent substituents as -CH<sub>3</sub>, -Cl, or -OCH<sub>3</sub> groups.

Exceptions to this unfavorable effect of blocking the amide group were the acetanilide (p-CONHC<sub>6</sub>H<sub>4</sub>NHCOCH<sub>3</sub>) and alcohol (p-CONHCONHC<sub>2</sub>H<sub>4</sub>OH, p-CONHCH<sub>2</sub>CHOHCHOH, p-CONHC<sub>2</sub>H<sub>4</sub>OH, and p-SO<sub>2</sub>NHC<sub>2</sub>H<sub>4</sub>OH) derivatives, with indices essentially the same as that of the parent amides.

The possibility at once suggests itself that these relatively non-toxic and effective amide substituted phenylarsine oxides, may find a direct application in the prophylaxis of syphilis. Experiments as yet incomplete, indicate that this may prove to be the case. The 4-CONH<sub>2</sub> compounds has proved to be completely effective in preventing infection when applied as late as four hours after the inoculation

of a superficial incision with an amount of spirochetes which represents approximately 10,000 infective doses. The time limits over which this prophylactic effect are observed, the minimum effective concentrations, and the possibility that this prophylaxis may be effective even if the drug is applied before inoculation, are now being studied. The local toxicity of these drugs when applied to mucous membranes will be studied by Dr. Calvery and those associated with him. Our own work indicates that their toxicity on intradermal injection parallels their systemic toxicity in mice and rabbits. On instillation for four consecutive days into the rabbit's conjunctiva, 2 per cent solutions of the  $\text{+SOCH}_2$  phenylarsine oxide in propylene glycol had no local irritating effect.

The gonococidal activity of the amide-substituted arsine oxide is now being studied by Justina Hill, and will be further studied by Miller. The former is using a technique which involves the addition of cysteine to stop the action of the drug prior to plating as a criterion of survival. The technique of Miller will entail repeated washings of the organisms to remove all excess arsenical before the drug is plated. The results obtained by Hill already indicate that despite the uniform activity of these amide-substituted arsine oxides against spirochetes, they differ widely in their gonococidal activity. A significant proportion of these compounds are sufficiently active against gonococci to suggest that they may be of prophylactic utility against that disease as well.

The virucidal activity of these compounds against lymphogrenuloma venereum is being studied by Reke. Approximately fifteen of these compounds are no longer available, inasmuch as the small amount prepared in our laboratory has been used for the assay of their toxicity and treponemidal activity. With the assistance of various pharmaceutical firms, adequate amounts of these compounds will be prepared to permit the assay of their gonococidal and virucidal activity. In addition, these compounds will be submitted to Doctors Combes and Greenblatt for the determination of their efficacy in the prevention of infection in human skin inoculated with chancroid (cultures of *H. ducreyi*).

Given so large a series of compounds of potential utility, it will obviously be impossible to study the effect of various ointment bases and various wetting agents on the prophylactic efficacy of each compound. Indeed, it will be a prohibitive chore to assay the prophylactic efficacy of this entire series even in rabbits. It is therefore planned to determine for a few selected compounds whether the treponemidal activity in vitro is a reasonable measure of prophylactic activity in vivo. That having been determined, the effect of varying the ointment base, and of various wetting agents on the prophylactic activity of a few representative compounds will be studied. In addition, Calvery has undertaken to determine the local toxicity of these compounds, and the degree to which they are absorbed from the skin or mucous membrane, as affected by the solvent, ointment base and wetting agent. The systemic toxicity of the compounds included in our series has already been determined in mice, and in the case of some representative compounds, in rabbits as well.

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Chairman's Comment:- Dr. McHoney reports that in his laboratory, prophylactic experiments have been carried on with napharsen, which is effective in a dilution of 1-1000; and is more effective than any other substance with which he has

worked. Attention was drawn to the instability of mapharsen, and the desirability of concentrating further effort on more stable compounds.

It was agreed that the arsenical compounds, or one or two of the more promising representatives of them, should be further studied as rapidly as possible as to their prophylactic effect in rabbit syphilis, utilizing these drugs both in solution and in ointments (to be prepared under the direction of Calvery), and that in view of the indications as to their possible over-all activity against syphilis, gonorrhoea and lymphogranuloma, they should be tested promptly against chancroid.

JUSTINA H. HILL

(a) The production of gonococcal infection in experimental animals:

1. The previously reported method of testicular inoculation of mice has been further studied. It has not been possible in 19 mouse passages to increase the virulence of the gonococcus for mice by this method. It is of value for the animal passage of cultures intended for experimental use, such cultures being obtained from the heart blood of mice dying from 6 to 8 hours after testicular inoculation.
2. Further study of this method has seemed less important than continued attempts to obtain either a true genital infection or a prolonged survival of gonococci on genital mucosa. The following groups of experiments have therefore been undertaken:

A. Pathologic Studies

- (1) studies of the normal genitalia in order to obtain exact information for correlation with the instrumental methods of inoculation being used,
  - (2) studies of the genitalia, male and female, after inoculation. This is important because smear and culture methods reveal information concerning only the surface flora of the mucosa.
- B. It has been found repeatedly that direct inoculation of the mouse vagina or male urethra is followed by disappearance of the gonococci within 2 hours. With this as a base line, experiments have been made to increase this survival time. Four methods are being used, as follows:
- (1) Inoculation of the preputial glands of the mouse. This is easily done either after a simple incision or by inoculation through the skin. Gonococci have been recovered 3 days after inoculation. This method is being intensively studied, with various modifications of the medium of suspension and of the resistance of the host (x-ray or vitamin A deficiency).
  - (2) Cystostomy. The effect of the diversion of the urine from passage through the urethra is being studied after cystostomy in the mouse. Aside from shock when the incision into the bladder is made, mice tolerate this operation well. Broth suspensions of gonococci have failed to survive 24 hours after urethral inoculations made 3 days after operation, but these experiments are being continued, with the modifications suggested under (1) above.
  - (3) Variation of the vehicle used for suspension of the inoculum.

On the basis of in vitro tests made by Mary E. Turner by Method A, as described under (b), but without cysteine, the following substances have been added in various concentrations to the suspension of gonococci used for the inoculation of the male urethra or vagina:

a. propylene glycol: (in vitro, slight action 1:4, none 1:8)

1. vaginal inoculation, full strength of 1:8 dilution of the drug, all mice positive cultures until 11th to 14th days.

2. urethral inoculation, full strength, no prolongation, 1:8 prolongation of positive cultures to 18th day.



further experimentation. The fact that better survival was generally obtained in the vagina may well be due to the greater ease with which the chemical agent can be applied to its mucosa than to that of the urothra.

It is seen from these experiments that prolongation of the survival of gonococci can be obtained by inoculation of the preputial glands, or, more markedly, by the use of propylene glycol or the other chemicals tested. It seems possible at this date to hope that by the use of one or another of these methods, or possibly by a combination of them, a method can be established by which valid tests of chemical prophylaxis can be studied on the genital mucosa of the mouse. Further experiments are being carried out as rapidly as possible.

(b) In vitro and in vivo tests of gonococidal substances.

Three methods are being compared for use as a rapid screening test:

1. Method A. Entirely in Vitro.

This was evolved primarily to test as rapidly as possible a number of arsenicals being studied by Dr. Eagle. The test is as follows:

A. Drug dilutions. These are made usually from a stock dilution of 1:2,000.

The medium of dilution is beef-heart infusion broth pH 7.2. The dilution series, beginning with 1:5,000, progresses by doubling, 1:1,280,000 usually being a satisfactory final dilution. Two ml. amounts of the dilutions are pipetted into sterile test tubes, triplicate tests being used for every dilution.

B. Inoculum. This is 0.1 ml. of a beef heart infusion broth suspension of 18 hour cultures of gonococci on beef heart infusion chocolate agar slants. The turbidity of the suspension is standardized by dilution to a reading of 95 on the green (No. 54) filter in a Klett-Summerson colorimeter. The suspension is made immediately before inoculation. In spite of this attempt to standardize the inocula, the resistance of the gonococci to the reference drug, phenylarsone oxide, varied from test to test. This is believed to be due in part to the clumping of the organisms, although the suspension is filtered through glass wool and thoroughly shaken with beads, and in part to fluctuations in the resistance of the organisms from day to day. Thus tests made on a given date are comparable, those made on different dates are not necessarily so, but in satisfactory repeated experiments the proportions between the action of the unknown and of the reference drug remain the same.

C. Test. The inoculated tubes are kept in an incubator at 36° C. for 2 hours. At the end of this time drug action is arrested by the addition of 0.1 ml. of a solution of cysteine hydrochloride, prepared as follows:

250 mgs. of cysteine hydrochloride, to which 3 drops of 0.1 % aqueous solution of brom-thymol-blue have been added, are dissolved slowly and with shaking, in about 10 ml. of N/7 NaOH, or until the first appearance of a blue color in the solution.

Since often more than 100 tubes are involved in a given experiment, 2 lots of 250 mgs. of cysteine hydrochloride are prepared and the second is dissolved half way through the addition of the cysteine hydrochloride, in order that it may be fresh.

Immediately after addition of the cysteine hydrochloride one 2 mm. loopful is spread upon one half of a beef heart infusion chocolate agar plate.

These plates are incubated at 36° C. for 48 hours (the 1st 24 hours in a carbon dioxide jar) and read. The end-point is taken as the highest dilution which prevents a # growth of the gonococcus. The degrees of growth are calculated by comparison with the 3 drug-free controls included for every drug. Those should read as ####. It was decided that because of the complications of the technical method, which involves considerable manipulation of the tubes, a reading of positive would include growth of more than 16 isolated colonies.

While the limitations of this test are fully recognized, it has provided a screening technique by which drugs can be compared. The technical difficulties of washing and centrifugalization methods necessitate the testing of a smaller number of drugs or dilutions than can be done by this method. To date more than 30 drugs have been given repeated testing by this method.

2. Method B. Entirely in Vivo (Modified Bang Method).

12 day chick embryos are opened and inoculated with 1 drop of the suspension prepared as in Method A. Two hours later 0.5 ml. of the drug is added per egg, at least 4 eggs per dilution: Two hours later 0.1 ml. of cysteine hydrochloride prepared as in Method A is added and the embryo is then washed 4 times with beef-heart infusion cysteine broth, by means of a pipette attached to gentle suction. The eggs are then incubated for 24 hours, the membrane is smeared and cultures for gonococci and the condition of the embryo is noted.

3. Method C. In vitro-in vivo Method.

The tests as in Method A are set up in centrifuge tubes. After 2 hours of incubation 0.1 ml. of cysteine hydrochloride is added, the tubes are centrifuged and the supernatants decanted. Two washings are then used, both in 10 ml. of beef-heart infusion cysteine broth. After the decantation of the second washing, one 2 ml. loopful of the sediment is streaked on  $\frac{1}{2}$  of a chocolate agar plate, the rest is suspended in 0.5 of the cysteine broth and placed on the membrane of the chick embryo. This is smeared and cultured after 24 hours and the condition of the embryo noted.

To date most of our experiments have been made with Method A. Within a short time it should be possible to evaluate the three methods and to decide which of them gives us the most satisfactory end-points for the comparison of arsenicals. If these methods are to be used for other types of drugs, either washing alone or the substitution of an appropriate chemical for the cysteine will have to be used.

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Chairman's Comment:- Discussion emphasized the point that in these experiments, and so far as is known for the first time, persistent gonococcal infection has been produced on the genital mucosa of animals. It is not yet clear whether this is accompanied by actual evidence of gonococcal disease. The results are preliminary only but are sufficiently promising to justify further vigorous study by Dr. Hill and for confirmation, in the laboratory of an independent observer (Dr. Miller).

Various suggestions were made to Dr. Hill for further study.

Emphasis was laid in discussion on the fact that certain arsenical compounds were found to be parasocidal by in vitro tests; and that work in this direction should be pushed in the effort to develop the over-all prophylactic agent.

The use of cysteine in the chick embryo test appears to afford a more accurate method of in vivo assay than the washing technic employed by Bang (see below); and within a few weeks the parallel use of in vitro tests with this in vivo technic should afford an indication of the desirability of continuing with the latter.

C. PHILLIP MILLER, UNIVERSITY OF CHICAGO

MEMORANDUM ON TESTING OF CHEMICAL PROPHYLACTICS AGAINST GONORRHEA

We have under consideration two types of chemical prophylaxis against gonococcal infection:

I. The oral administration of a chemo-therapeutic agent such as sulfathiazole which acts by its presence in the body fluids of the host, to destroy the gonococci which have already penetrated the external layer of the mucosa (and possibly also those gonococci which are still on the surface and available to the action of the drug secreted in the urine). The laboratory tests on such a drug seem to me best carried out in vivo. They can be designed to determine the ability of a drug to prevent experimental gonococcal infection from developing into a generalized and fatal sepsis and to that extent simulate the action of the drug in man. The test animal should be small, cheap, easily handled and available in adequate numbers. The white mouse is the animal of choice since it can be infected with gonococci by two methods: the intratesticular inoculation described by Hill, and the intraperitoneal infection by means of mucin worked out in my laboratory. I am naturally partial to the latter method because I am familiar with it. It requires care and attention to detail but is really quite easy to carry out. Gonococci from a young, actively growing culture are suspended in 4 percent mucin and injected in 1 cc. quantities into the peritoneal cavity of white mice. A generalized peritonitis develops and is followed by sepsis and death. Gonococci can be recovered from the heart's blood; in fact, it is a culture of heart's blood which is used for each succeeding mouse passage. By persistent mouse passage for many months the virulence of several strains has been enhanced, one of them to a point where a few hundred gonococci now suffice to initiate a lethal infection--often less than one hundred.

This method can be exploited for the testing of immune sera or of chemo-therapeutic agents. Drugs can be given directly into the stomach by catheter or injected under the skin or into a tail vein, or, if not too irritating, directly into the peritoneal cavity. For instance, 15 mgr. of sulfathiazole administered subcutaneously in 3 doses will save the lives of mice infected with 100,000 M.L.D. It does this by preventing the infection from becoming generalized and assisting the host in bringing it under control.

II. The other type of chemical prophylaxis is the local application of an antiseptic whose purpose is to destroy the gonococci on the surface before they are able to penetrate it and invade the tissues of the host. This is really a special case of the general problem of skin disinfection, a subject on which much has been written. Our problem is simplified because we know just what pathogen we want to destroy and the surfaces on which it is located. It narrows down to the selection of a method for determining the relative gonococcidal activity of non-irritating germicides.

The ideal method would be an experimental gonococcal infection of some easily accessible mucous membrane to which the chemical could be applied. Unfortunately no laboratory animal has been found to be susceptible to that kind of inoculation. I myself have made innumerable attempts over the course of many years.

I still have in mind three possibilities which deserve trial:

(a) The conjunctiva of mice suffering from Vitamin A deficiency. I have a colony of mice on such a diet now.

(b) Conjunctivae damaged by ultra-violet radiation.

(c) Rabbits infected with myxoma virus which gives them a mild conjunctivitis. Preliminary experiments on such rabbits whose tears have been suppressed by atropine suggest that this method may have possibilities, but experience has taught me to forego optimism at this stage.

III. Of the many methods devised for the testing of germicides in vitro, most have used as test organisms bacteria which are hardy and easy to cultivate on artificial media, such as the staphylococcus or colon bacillus. In the case of the gonococcus, however, special difficulties arise from its growth requirements and the fact that it easily dies out if these are not satisfactorily met. The method I prefer was originally worked out for testing the action of germicides on meningococcus, an organism almost as fastidious. Equal numbers of gonococci are suspended in varying concentrations of the chemical and at stated intervals are removed by centrifugation, washed and sedimented again. Approximately equal quantities of each sediment are streaked onto the surface of a freshly poured blood plate. The number of colonies developing indicate the number of gonococci still alive and thereby gives a rough estimate of the proportion of viable members of the original bacterial population which have survived exposure to the germicide at that temperature for that length of time.

This method seems to me to eliminate any bacteriostatic action of the chemical and, by giving each surviving gonococcus its optimum environment for multiplication, to test most rigidly the actual killing power of the germicide. Attempts have been made to increase the accuracy by various means to permit more precise enumeration of colony counts, etc., but it was found that very little improvement resulted from a great deal of additional effort.

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Chairman's Comment: General discussion indicated that:

1. Dr. Miller's suggestions for experimental gonococcal infection in animals should be pursued, plus an attempt to establish conjunctival infection in suitable animals whose lacrimal glands have been surgically removed.
2. Dr. Miller should attempt to verify Dr. Hill's apparent success in establishing gonococcal infection on the genital mucosa of mice.
3. Dr. Miller's in vitro technic should be further employed in an effort to screen out potentially gonococidal substances (especially arsenicals) suitable for further study.

TABLE 1 (MILLER)

**ACTION OF SODIUM SULFATHIAZOLE ON EXPERIMENTAL GONOCOCCAL INFECTION IN MICE**  
 Administered subcutaneously before, 3 and 6 hrs. after inoculation.

Approximate No. Gonococci injected	1,000,000	100,000	10,000	1,000	100	10	1	None	
								Mucin Controls	
								1.0 cc.	1.5 cc
Total dose 15 mgm.	125*	S	S						
	S	S	S						
	S	S	S						
Total dose 30 mgm.	S	S	S						
	S	S	S						
	S	S	S						
Controls		<20	<20	23	52	52	S	S	20
		<20	26	52	S	S	S	S	S
Total dose 15 mgm.	S	45	S						
	S	S	S						
	S	S	S						
Controls	<22	<22	<22	23	26	45	S	S	S
	<22	26	26	23	45	S	S	S	S

\* Numbers indicate time of death in hours after inoculation.  
 S= Survived.

ALFRED COHN, DEPARTMENT OF HEALTH, CITY OF NEW YORK

MEMORANDUM ON LOCAL SULFONAMIDE TREATMENT OF ACUTE GONOCOCCAL URETHRITIS

A limited clinical investigation on the local effect of sulfonamides in acute gonorrhoea in the male was initiated in 1942 by the Gonococcus Research Unit of the Department of Health, City of New York. The patients selected for this study were all males with untreated gonococcal infections, usually of not longer than 3 days' duration. Smears and cultures of the urethral discharge were taken before treatment and at frequent intervals throughout the period of observation. At each examination the amount and appearance of the discharge and the results of the two-glass urine test were recorded. Determinations of the sulfathiazole level in the blood, taken 12 or 24 hours after the intra-urethral instillation of the sulfonamide, were performed in some cases. However, the amount of the drug in the blood was so low as to prohibit accurate determination, and this procedure was soon discontinued.

The first compound to be tested was an ointment containing 20% sodium sulfathiazole. It was obtained from Dr. Thompson, of the Warner Institute, New York and was dispensed in tubes each containing 3 cc. Preliminary experiments conducted by Dr. Sanders at the Letchworth Village Institution showed that the instillation of 3 cc. of this ointment did not produce any local irritation of the normal male urethra or any systemic toxic by-effects.

Fourteen ambulatory male patients were treated by the intra-urethral instillation of this 20% sodium sulfathiazole ointment. The average course of treatment consisted of 10 instillations over a period of 5 days.

The procedure in each case was as follows: Patients were instructed to urinate prior to each instillation and were advised to refrain from voiding for as long as possible thereafter. The compound was instilled and the urethra massaged after each injection. The men received one treatment at the clinic and were told to repeat it at home 8 to 12 hours later. Instructions as to local and general hygiene were given; the patients were advised to restrict fluid intake as far as possible.

Eight of the 14 cases showed clinical and bacteriologic improvement. Definite clinical improvement was frequently observed. After the 3rd or 4th instillation, the original profuse urethral discharge diminished and changed to a thin watery or serous discharge. The first urine usually cleared up during the same interval. Bacteriologic improvement, however, showed no regularity in regard to the time at which the culture became gonococcus negative. Some reversals from positive to negative occurred as early as after the 2nd or 3rd instillation, but most cases were not altered before the 6th or 7th instillation.

If a follow-up period of 3 or 4 weeks with negative bacteriologic and clinical findings is accepted as adequate, 7 patients may be considered cured. Two of these, however, were originally diagnosed as gonococcus positive from the smear alone, since the corresponding cultures were negative due to a defect in the air-tight box we used for maintaining a CO<sub>2</sub> atmosphere.

In 6 cases, the instillation of the 20% sodium sulfathiazole ointment had no effect. Cultures remained positive, but the originally profuse purulent discharge of some patients changed to a slight mucoid one.

The majority of patients complained of slight and temporary burning or stinging sensation during the actual intra-urethral instillation of the ointment. This sensation ceased shortly after the instillation and was less frequent during the progress of treatment. It was assumed that this symptom was due to distention of the inflamed urethra, especially since the sensation never occurred during instillation into a normal urethra.

Three additional cases of acute gonococcal infection were used as controls. They received instillation of the same ointment base without sulfathiazole. No effect on the course of the infection could be observed.

The results obtained thus far indicate a favorable effect of the local application of a sulfonamide compound in gonococcal infection.

In a few male patients with acute gonococcal infections the effect of sulfonamides administered by inunction was studied. A certain amount of 20% sodium sulfathiazole finely dissolved in a semi-solid ointment vehicle was gently massaged into the skin, until all or most of the material appeared to be absorbed into the skin. Repeated inunctions were without any bacteriologic or therapeutic effect.

Three additional patients were treated by inunction of sulfathiazole ointments prepared by the Wallace Laboratories Inc., New Brunswick, N. J. In these ointments, a surface action agent was incorporated, in order to enhance penetration. There was no therapeutic effect, and sulfathiazole could not be detected in the blood of these three cases.

Recent studies of the Gonococcus Research Unit have again focussed upon the local application of homogeneous colloidal dispersions of sulfathiazole. These compounds, according to the Wallace Laboratories, contain 0.12% of a percentage of a wetting agent (sodium lauryl sulfate) which makes the dispersions more homogeneous and stable. No results can thus far be reported.

The observations here reported are too incomplete to allow any conclusions to be drawn. It appears safe to state, however, that the local application of sulfonamides is followed in a considerable percentage of cases, by definite clinical and bacteriologic improvement, and by apparent cure in those cases where an adequate follow-up was possible. Massaging into the skin ointments containing up to 20% sulfonamides had no apparent effect on the course of the infection.

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Chairman's Comment: There ensued a discussion of the relationship of this group to pharmaceutical houses. It was agreed that investigators collaborating with the group should confine their studies to substances supplied through the group.

The question was raised as to possible sensitization against the sulfonamides from their local use. Dr. Stokes referred to an unpublished paper by Pillsbury and Livingood shortly to appear in the J.A.M.A., which cites a dozen examples of sulfonamide sensitization through inunction with sulfonamide ointments. No other information apparently exists. The Chairman remarked that it was hoped to organize studies on sulfonamide sensitization through the Surgeon General, U. S. Army, in certain Army Camps.

It was agreed that studies similar to this one of Dr. Cohn's should be pursued on a much larger scale. Arrangements to study ointments prepared by Dr.

Thompson, i.e., 5 and 20 % sulfanilamide and 5 and 20% sulfathiazole are already planned in the clinics of Drs. Cohn, Cox and Diobert. Others should follow.

FREDERIK B. BANG, M. D., PRINCETON, N. J.

EXPERIMENTAL PROPHYLAXIS OF GONOCOCCAL INFECTIONS\*

Gonorrhoea, from the point of view of the pathologist, should be considered as a superficial infection of certain mucous surfaces, rather than as a specific infection of any one structure. As such it usually remains in the superficial layers of the mucous membrane, provokes a moderate leucocytic response, and is eventually overcome unless chance or manipulation introduces the infection into new areas.

Infection of the chorioallantoic membrane is just such an infection. It may readily be transferred from one animal to another, it produces a superficial infection in which the organisms fail to penetrate the tissues, and finally a moderate leucocytic response with phagocytosis of the gonococci. Depending on the number and virulence of the organisms used, the infection may be transient and self-limited, or may progress to kill the embryo through the elaboration of toxins. Certain strains which through continued passage have become highly adapted to the chick embryo will also produce septicemia and a rare meningitis, again reproducing the story of the natural infection.

In order to use the gonococcus infection of the chorioallantoic membrane in the study of prophylactics several requirements should be fulfilled. (1) The procedure must in general resemble actual prophylaxis. (2) Known efficient prophylactic agents (protargol, argyrol) should be effective by this technique. (3) The majority of control embryos must remain infected after the same gentle washing with saline that is necessary to clean away the drug tested in the experimental series. (4) The majority of embryos which are cured of their infection should remain alive. It has been possible to comply with these standards.

Prophylaxis in the human is really a local treatment of an infection in which the gonococci have just begun to multiply and spread. It is not known what happens to the gonococci within the first few hours of infection, and our guess must be based on studies of the experimental infection of convicts 33, 38 and 72 hours before execution. Since these studies demonstrate only a slight penetration of the cocci into the interstices between the columnar epithelial cells in the last case, we may assume that an infection of a few hours' duration is limited to the surface. Thus local treatment of both embryo and human infections would present the same problems.

Procedure

Embryos are opened by cutting a window in the side of the shell and allowing the membrane to settle. The chorioallantoic membrane of 12 day old embryos is infected with one drop of a saline suspension of gonococci made by adding about 3 cc. of saline to a heated blood agar slant inoculated 18 to 24 hours previously. Embryos 12 instead of 10 days old are used because the tougher membrane withstands manipulation and because the older embryo is less likely to die following infection. The artificial window is covered with a piece of Scotch tape and the embryo is reincubated.

\* In Dr. Bang's absence, this report was read by the Chairman. The report as originally submitted is shortened here by the omission of unimportant or repetitious paragraphs and of the text figures and bibliography.

ed at 35° C. for 2 to 3 hours. The Scotch tape is then turned back, exposing the artificial air sac, and the drug to be tested is either dropped on the membrane or, if too viscous, is spread over the membrane by placing the tip of the pipette on the membrane and moving it all over the exposed surface. Two minutes later the drug is sucked off the membrane as follows: a pocket is formed in the middle of the membrane by pressing down gently with a large pipette, and the fluid which collects around the pipette tip is sucked off with a capillary pipette attached to gentle suction (Text-fig. 1). The membrane is then washed twice with sterile saline. Care must be taken to exclude membranes with holes. The embryo is reincubated, and is tested the next day for infection both by smear (Gram stain) and by culture on heated blood agar plates. The cultures are read on the 1st and 2nd days and are then tested for the oxydase reaction with p-aminodimethylaniline monohydrochloride. In each test an equal number of controls is treated by washing with saline alone. These must be positive or the experiment is discarded. Of a total of 1050 control embryos used, 67, or 6 per cent, failed to show infection with gonococci. The mortality of the embryos due to the mechanical procedures may be judged by noting that of 383 embryos treated with 0.1 per cent of either sulfonamides or arsenicals only 58 (15 per cent) died. 3.8 per cent (198 of 4980) of the embryos were discarded because of contamination acquired during manipulation.

Strains of gonococci used in these experiments were isolated from cases of acute gonorrhoeal urethritis at Fort Dix. They were identified by typical translucent colonies on heated blood agar, by their failure to grow on plain agar and at room temperature, and by the usual fermentation reactions and morphology with Gram staining. Most of the work here reported was done with one strain, which was used at first after 25 passages on the embryo, later without embryo passage. The use of other strains will be specifically referred to in the paper.

In several ways this test for the prophylactic value of a drug is more rigorous than that imposed by actual practice. (1) A larger dose of gonococci is used than that which probably infects the usual urethra. (2) The infection of the embryo is allowed to develop for 2 to 3 hours, while many prophylactics are given much sooner after exposure. (3) The drug is allowed to remain on the membrane for only 2 minutes, while in the standard prophylactic procedure argyrol is kept in the urethra for 5 minutes. (4) The drug is washed off the membrane immediately, while in the human there is no comparable washing effect until the next urination. These differences explain the fact that argyrol and protargol were only 50 to 60 per cent effective in our experiments, while actual practice indicates a much higher (100 per cent ?) effectiveness.

### RESULTS

Table I shows the effect of treatment of the membrane infection with 2 percent argyrol and protargol solutions. Both of these drugs were consistently effective in preventing the development of infection in about 50 to 60 per cent of the cases. No significant difference was demonstrated between 2, 5 and 10 minutes of treatment. It was also demonstrated that treatment of the membrane several hours before attempting infection prevented such infection. This would indicate that even though the drug is allowed to remain in contact with the membrane for only 2 minutes and is then washed off, enough drug is fixed to the tissue to then prevent multiplication of the gonococci. The failure to demonstrate an effect of time would indicate that the silver compounds were fixed by the tissue rather rapidly.

It was soon clear that mere water solutions of the sulfonamides would not cure as high a percentage of embryos as did the argyrol, nor did the addition of solutions containing both sulfanilamide and azochloramide sufficiently increase the effectiveness (see Table VII).

Since the limiting factor seemed to be the concentration of the drug used, we next tried concentrated (10-30 per cent) solutions of sulfanilamide and sulfathiazole. These were made by Wallace Laboratories by adding the drug to a base (propylene glycol), the high concentration being attained by the addition of a solubilizer of approximately twice the weight of the drug. These solutions consistently cured 90 to 100 per cent of the experimental infections.

Such solutions are highly viscous, absorb water from tissues rapidly, and much of the drug is precipitated on contact with water. Since solutions of lower concentration lack much of this damaging effect, we have determined the 50 per cent effective endpoint for each of a number of drugs. This is done by the accepted statistical procedure of accumulating positive and negative results in order to smooth the curve. It may be illustrated by the data obtained in testing different concentrations of 434<sup>4</sup>. Table II shows in column e the actual number of embryos cured at the different concentrations. Columns e and f show the figures obtained if we assume that embryos cured at lower dilutions of the drug would have been cured at the next higher concentration, and that infected embryos which resisted higher concentrations would have resisted the low concentrations. The effect of this procedure is to smooth the curve obtained (Chart 1) and make the data more accurate. It can of course be practiced only if the data in themselves actually demonstrate that increasing concentrations are more effective.

#### Effect of Solvent

Propylene glycol was used as the standard solvent because it carries higher concentrations of drug than does water. It was used in the comparison of all the drugs here tested. Other workers using different techniques found propylene glycol too toxic when injected into the egg and therefore chose triethylene glycol. A comparison of the effect of the two solvents on the efficiency of different drugs is presented in Table III, which includes a number of separate experiments.

The accumulated results for 434 are shown in Chart 1. It will be noted that the use of triethylene glycol consistently lowered the efficacy of 434, neoarsphonamide and sulfathiazole.

The Subcommittee on Venereal Diseases, of the National Research Council, hopes to develop one prophylactic agent which will be active against all four of the common venereal diseases. Since the sulfonamides have no known effect against the treponemas of syphilis, it seemed worth while to test drugs which might be expected to act against both treponemas and gonococci. Two compounds which combine an arsenical and a sulfonamide ring, 434 and 524<sup>6</sup>, were furnished by Dr. G. W. Hake of the Squibb Institute. They had been synthesized by Mr. W. A. Lott of the same organization. Both of these compounds were found to be highly effective against gonococci on the choricallantoic membrane (Table IV, Charts 1 and 2).

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- ◆ 434 = 4, 4'-disulfanilamido-arsino-benzene.
  - ◆ 524 = 4, 4'-disulfanilamido-arsino-oxide.

The efficacy of these compounds made a comparison with other arsenicals necessary. The results of these comparisons are presented in Table IV and Chart 2. In general arsenicals here tested are more effective than the three sulfonamides. Certain precautions must be observed in interpreting these curves. First, the point of clearest differentiation is the 50 per cent endpoint, and little or no attention may be paid to the curves at either the lower or the upper end, for here chance plays too large a part. Second, if two curves cross anywhere near the middle, the number of embryos tested has been inadequate to differentiate these drugs. Thus, mapharsen 434, neocarsphonamine and chlorarsine cannot be differentiated. Sulpharsphonamine, which is more slowly oxidized into the form active against treponemas, is here the least effective of the arsenicals; the fact that it is at all active indicates that it is broken down by the embryo tissues.

#### Effect of Strain Used

It is possible to demonstrate that sulfanilamide-resistant strains of gonococci retain their resistance on the embryo. Table V presents the results of a number of tests using two different strains, both recently isolated. McV was isolated from a patient who had failed to respond to 5 days of sulfathiazole, while Sa was taken from an untreated case of acute urothrits. No striking difference is demonstrated between these two strains.

#### DISCUSSION

The validity of comparing the results of experiments on one drug one day with those of another drug on another day may rightly be questioned. However, it was always our practice to compare each day the effect of different concentrations of the drug tested with a standard preparation of a better known one. During the preliminary experiments this standard was ergyrol. Later, when testing arsenicals and sulfonamides, we used 0.2 per cent of 434 in propylene glycol. Results of these individual day by day experiments all agree with the overall results presented in Table IV. Space and the need for clarity make publication of these data inadvisable.

The purpose of these experiments was, of course, to furnish data for new local prophylactic agents to be used in preventing the development of gonorrhoea. It is always impossible to transpose the results of animal experimentation directly to humans without a careful re-evaluation. This will be true of the results here reported. It is desirable to examine the differences in the techniques used in the treatment of the experimental and human infections. The similarity of approach was emphasized in the introduction, but no great difference remains. The infection of the chorioallantoic membrane is very extensive compared to the size of the host. Several square centimeters are affected, and the volume of the average egg is about 50 cc. On the other hand, the human infection usually does not cover a much larger absolute area than the embryo infection, but the volume of man is incomparably greater. This immediately introduces the problem of local versus systemic treatment, for it would be possible to treat infected embryos locally with enough drug to be absorbed in sufficient quantities to act systemically rather than locally. This is likely in the human where the relatively small amount absorbed would be diluted in the greater body volume. Such considerations would hold for any animal in which the body surface infected by gonococci was relatively large.

The evidence on the question of the local versus the systemic action of several of these drugs is presented by three different types of experiment. First, both protargol and argyrol, which are very poorly absorbed, have a definite curative effect on these early infections. This action is probably entirely local. Second, we may compare the effect of treating similarly infected embryos locally and by injection into the embryo. The results of these treatments with four different drugs are presented in Table VI and plotted for 434 in Chart 3. It will be noted that treatment by injection is twice as effective as local treatment. If half the drug is removed by suction and washing, in these given local treatment the curves would correspond; if much more is actually removed, it would indicate that membranous treatment is more effective. This can only be settled by studies on the absorption and distribution of the drugs. Table VI indicates that these results may be different for different drugs.

A third line of evidence is furnished by the results of comparing the known synergistic action of sulfanilamide and azochloramide with the results of the local treatment of membranous infections (Table VII). This table shows that little increased effectiveness is contributed by the addition of azochloramide. This means that the synergistic effect found in vitro for these compounds is not reproduced by local treatment.

Finally, it is worth noting that in vitro tests on a number of bacteria have demonstrated the high degree of effectiveness of certain arsenicals.

These different points suggest that part of the results obtained by the local treatment of the membranous infection is actually due to the local action of the drug. On the other hand, the fact that these arsenicals and sulfonamides do act systemically in the embryo when injected into the egg, and the long slope of the curves obtained (Charts 1 and 2) suggest that at least a part of it is due to a later systemic effect. Only thorough study of the absorption of the different drugs inoculated by different routes will settle the question of the relative importance of each of these.

#### SUMMARY

The experimental infection of the chorionallantoic membrane of 12 day embryos with gonococci has been used to study the prophylactic value of argyrol, protargol, solutions of sulfonamides and arsenicals. This is accomplished by placing the drug directly on the 2 to 3 hour old membranous infection, removing it 2 minutes later by suction and washing with saline. Controls treated with saline alone remain infected 94 per cent of the time.

Argyrol and protargol are effective in 50 to 60 per cent of the infections. Highly concentrated (10 per cent +) solutions of all the sulfonamides and arsenicals in propylene glycol are effective in more than 90 per cent of the infections. The relative value of these drugs determined by the 50 per cent endpoint in order of increasing efficiency is: sulfanilamide, sulfaguanidine, sulfathiazole, sulpharsphenamine, 434, mapharsen, neocarsphenamine, chlorarsine and 524. Sulpharsphenamine and sulfathiazole were not clearly differentiated. The four arsenicals - mapharsen, 434, neocarsphenamine and chlorarsine - also had the same order of efficacy. The effect of the drug is influenced by the type of solvent used.

The available evidence indicates that part of the curative effect is local.

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Chairman's Comment:--General discussion threw doubt on whether effect of medicaments in the chick embryo could be regarded as in vitro or in vivo effect.

Attention was drawn to the fact that no mention is made on the effect of solvents alone (e. g., propylene glycol).

The question was raised of the relative merits of purely in vitro experiments with the chick embryo technic. Dr. Hill reports that parallel chick and in vitro plating experiments are being carried out in her laboratory and that an answer should be available in a few weeks as to whether one method holds any advantage over the other.

TABLE I

EFFECT OF 2 PER CENT ARGYROL AND PROTARGOL SOLUTIONS

STRAIN	ARGYROL						PROTARGOL					
	2 min.		5 min.		10 min.		2 min.		5 min.		10 min.	
	P	N	P	N	P	N	P	N	P	N	P	N
Sa	12	10	8	16			7	13	9	16		
Fo	6	8	3	3			1	4	2	5		
McV	8	4	4	3	4	2	8	17	6	2	6	11
Total	26	22	15	22	4	2	16	34	17	23	6	11
Per cent sured	46		59		33		68		57		65	

TABLE II

THE EFFECT OF 434 ON THE LOCAL TREATMENT OF GONOCOCCAL INFECTION  
OF THE CHORIOALLANTOIC MEMBRANE

a	b	c	d	e	f	
CONCENTRATION OF DRUG (PER CENT)	ACTUAL NO. OF EMBRYOS		PER CENT POSITIVE	ACCUMULATED		ADJUSTED PER CENT POSITIVE
	P	N		P	N	
10	1	33	3	1	260	0.4
2	0	58	0	1	227	0.4
1	2	11	15	3	169	1.8
0.4	0	10	0	3	158	1.9
0.2	14	99	12	17	148	10.3
0.1	7	19	28	24	49	32.9
0.02	48	27	64	72	30	70.6
0.01	13	2	87	85	3	96.6
0.002	12	1	96	97	1	99.0
0.0002	7	0	100	104	0	100.0

TABLE III

THE EFFECT OF TWO SOLVENTS ON THE EFFICACY OF DRUGS

DRUG	SOLVENT	NUMBER OF THERYCS																	
		CONCENTRATION OF DRUG (PER CENT)																	
		1.0		0.5		0.3		0.25		0.1		0.05		0.03		0.025			
P	N	P	N	P	N	P	N	P	N	P	N	P	N	P	N	P	N		
434	Propylene			2	8	0	7	0	10						1	6			
	Triethylene			4	5	1	7	4	2			12	3	6	2	12	3		
Neocarsphenamine	Propylene					0	7								4	3			
	Triethylene					2	6								7	1			
Sulfathiazole	Propylene	5	3									7	1						
	Triethylene	8	0									6	1						

TABLE IV  
THE EFFECT OF DIFFERENT CONCENTRATIONS OF DRUGS IN PROPYLENE GLYCOL ON THE GONOCOCCAL

INFECTION OF THE CHORIOALLANTOIC MEMBRANE

	NUMBER OF EMERYOS										CONCENTRATION OF DRUG (PER CENT)																							
	10	3	2	1	0.4	0.3	0.2	0.1	0.03	0.02	0.01	0.004	0.002	0.001	0.0002	P	N	P	H	P	N	P	N	P	N	P	N	P	N	P	N	P	N	
Sulfanilamide	4	19	10	11	9	0	6	4																										
Sulfaguanidine	1	12	7	20	123	4																												
Sulfathiazole	1	23	4	25	1	6	42	30																										
Sulpharsphenamine			9	14			13	17																										
434	1	33	0	58	2	11	0	10	14	99	7	19	48	27	13	2	12	1																
Neosarsphenamine			2	24					1	23			8	14																				
Mapharsen			0	2					10	25			11	12																				
Chlorarsine			0	19	7	18			1	25	0	6	8	12	5	2																		
524												4	38																					

TABIE V

A COMPARISON OF THE EFFECT OF DRUGS ON TWO STRAINS OF GONOCOCCI

STRAIN .....	MoV				Sa			
	CONCENTRATION OF DRUG (PER CENT)							
DRUG	0.1		0.01		0.1		0.01	
	P	N	P	N	P	N	P	N
Chlorarsine	1	15	4	11	2	12	5	7
Neocarsphenamine			1	3			1	3
434	0	14	9	5	1	14	5	7
Total	1	29	14	19	3	26	11	17
Per cent cured	96.6		57.5		89.6		60.7	

TABLE VI

A COMPARISON OF LOCAL AND SYSTEMIC TREATMENT

DRUG	TREATMENT	NUMBER OF EMBRYOS							
		CONCENTRATION OF DRUG (PER CENT) *							
		0.5		0.2		0.05		0.02	
		P	N	P	N	P	N	P	N
Sulfaguanidine	Membranal			11	2			24	2
	Injection			8	2			20	5
Sulpharaphenamine	Membranal							25	5
	Injection							26	1
Neosarsphenamine	Membranal	1	17			1	5		
	Injection	4	17			3	0		

\* These figures refer to 0.5 cc. of the solution placed on the membrane. When injected, 0.05 cc. of a solution 10 times as concentrated was used.

THE EFFECT OF INJECTING 0.05 cc. OF 434 INTO EMBRYOS

CONCENTRATION ( PER CENT)	NUMBER OF EMBRYOS *	
	P	N
5	2	13
1	2	11
0.5	0	5
0.2	21	11
0.1	17	12
0.02	8	0

\* These figures are presented in Chart 3 and should be compared with Table II where 0.5 cc. of the same drug is put on the membrane, then removed.

TABLE VII

THE EFFECT OF A COMBINATION OF SULFANILAMIDE, AZOCHLORAMIDE, AND A DETERGENT ON CONGOCCAL INFECTIONS OF THE CHORIOALLANTOIC MEMBRANE\*

CONTROLS		NUMBER OF EMBRYOS TREATED WITH						
		SULFANILAMIDE AND TETRADECYLSULFATE		SULFANILAMIDE, AZOCHLORAMIDE, AND TETRADECYLSULFATE		AZOCHLORAMIDE AND TETRADECYLSULFATE		
P	N	P	N	P	N	P	N	
11	0	9	4	8	5	12	1	
13	0	12	2	12	5	15	0	
14	0	10	5	12	5	14	1	
12	0	10	3	6	8	12	3	
9	0	16	5	11	11	19	3	
Total----- 59		0	57	19	49	31	72	8
Per cent cured---0		25		38.7		10		

\* Used locally. Sulfanilamide, 1:145; azochloramide, 1:10,000; sodium tetradecylsulfate, 1:800.

Notes: Since the per cent of embryos cured by azochloramide and by sulfanilamide alone when added together equals the per cent cured when these drugs are used together, we have no evidence of synergism.

REPORT OF PROGRESS IN HUMAN EXPERIMENTATION IN GONORRHOEA

The Chairman read extracts from the Minutes of a Conference on Chemical and Chemotherapeutic Prophylaxis in Human Volunteers held in Washington on December 1942. These Minutes have already been circulated and are not herewith reproduced. Proposals for O.S.R.D. contract have been submitted by Miller, Cohn and Carpenter for work in the prisons of Illinois, New York and Georgia, respectively. These proposals have been approved by the subcommittee on Venereal Diseases and the Committee on Medicine and are now under consideration by C M R - O. S. R. D. Final decision will probably hinge first on the public interest (political expediency) and subsequently on the legality of such experimentation. Pending decision by O. S. R. D. formal negotiations with State authorities are in obedience.

The sense of the present Conference was that such experimentation was urgently desirable and should be carried out as promptly as possible.

GEOFFREY RAKE AND HELEN P. JONES

THE TESTING OF VIRUCIDAL SUBSTANCES

Earlier studies from this and other laboratories had indicated that the sulfonamides, and particularly sulfadiazine and sulfathiazole, are highly effective against the agent of lymphogranuloma venereum *in vivo*. Despite the statements of other investigators that the drugs were not virucidal, our own investigations, carried out in mice, indicated that if sufficiently high blood levels were attained and maintained, virucidal action did occur. These experimental results in animals, particularly in mice and guinea pigs, confirmed the clinical successes obtained with the sulfonamides in the treatment of lymphogranuloma venereum in man.

In the studies to be reported here use has been made of the yolk-sac route of inoculation in the chick embryo, a technique of great delicacy in detecting small numbers of the infective agent of lymphogranuloma venereum. These studies can be divided into three groups, namely, those dealing with (a) sulfonamides (b) arsenicals, and (c) other antibiotic substances.

Sulfonamides. In one group of experiments different concentrations of drugs have been incubated with approximately 500,000 infective units of the agent in beef heart broth usually for a period of one hour at 37° C. The drug-agent mixtures were then inoculated into the yolk-sacs of embryos without further manipulation. Under these conditions definite virucidal activity was obtained (Table I).

TABLE I

Concentration of drug in mg per 100 ml	0.5 mg.	2.5 mg	5 mg	25 mg	50 mg	75 mg	100 mg	250 mg
Sulfadiazine	14/14	-	20/28	12/23	-	7/17	-	-
Sulfathiazole	10/10	5/5	22/27	17/28	3/5	-	6/17	-
Sulfanilamide	-	-	5/5	14/14	5/5	-	-	10/10
Sulfapyridine	-	-	5/5	13/13	5/5	-	4/7	-
Sulfaguanidine	-	-	5/5	10/10	4/5	-	7/9	-

14/14 = 14 eggs infected out of 14 inoculated.

These results summarize several experiments.

It will be seen that both sulfadiazine and sulfathiazole were virucidal - 29% and 18% respectively - at 5 mg per 100 ml (or .05 mg per 500,000 infective units) while sulfapyridine showed virucidal activity (43%) at 100 mg per 100 ml (or 1.0 mg per 500,000 infective units), sulfaguanidine showed virucidal activity (22%) at 100 mg per 100 ml (or 1 mg per 500,000 infective units) and sulfanilamide showed no

virucidal activity at 250 mg per 100 ml (or 2.5 mg per 500,000 infective units). The 50 per cent end-point was approximately 25 mg per 100 ml for sulfadiazine and 33 mg per 100 ml for sulfathiazole. Even with the lowest concentrations tested there was some virustatic action as shown by delay in death of the eggs receiving drug-agent mixtures as compared to the controls receiving agent alone. In the above cases yolk-sacs of eggs which died were smeared, stained and examined for virus. Eggs which survived were opened on the 21st day and similarly examined for virus. In subsequent experiments, described below, the true virucidal activity was further demonstrated by passing negative yolk-sacs through two passages in normal embryos by the yolk-sac technique.

In the above experiments it is clear that although only small amounts of drug are involved, the test cannot be regarded as an index of in vitro activity since no attempt has been made to separate drug from agent before inoculation. In subsequent experiments, therefore, a technique was evolved in which as much as possible of the drug was removed from the agent before inoculation.

In these experiments high concentrations of sulfonamides were attained by primary dilution in 80% triethylene glycol and 20% torgitol penetrant '7' 1/1000 in water. Dilutions of the drugs were made as required in distilled water. Equal parts of a given drug concentration were mixed with equal parts of a  $10^{-2}$  suspension of a heavily infected yolk-sac from a moribund embryo (approximately 1,000,000 infective units per ml). As a control, distilled water replaced the dilution of drug. In other controls equivalent or even larger amounts of the solvent in distilled water were mixed with equal parts of the virus suspension. These mixtures were incubated at 37°C for 1, 2½, or 3 hours. Three ml amounts of the mixtures were then centrifuged at 18,000 r.p.m. for 1 hour in the cold. The supernatant was discarded and the sediment resuspended in 5 ml broth. The centrifugation and washing were repeated twice more and the final or third resuspension made in 6 ml of broth. Each ml of this then contained  $1/4 \times 10^{-2}$  of the original yolk-sac suspension or approximately 250,000 infective units. Six-day embryos were inoculated by the yolk-sac route with 1 ml each of the final suspension.

Estimations of the amounts of sulfonamide remaining after such manipulations were made. In three cases in which the original mixture contained 2 gm ST per 100 ml the final resuspended sediment as used for inoculation was found to contain .115 mg, .068 mg and .062 mg. per 100 ml. In another case in which the original mixture contained 4 gm ST per 100 ml, the final resuspended sediment as used for inoculation contained .071 mg ST per 100 ml. The supernatant from the second sediment contained 38.8 mg ST and from the final sediment 0.78 mg ST per 100 ml. The amount of sulfathiazole remaining in the final inoculum is very small (especially in relation to the heavy inoculum of agent), and it appears to be constant in amount. This may indicate that it is bound to the agent and other components of the final sediment.

With incubation for only 1 hour, no virucidal action could be demonstrated although there was some virustasis (Table II). Such virustasis occurred with very large amounts of sulfathiazole--1 or 2 g per 100 ml or with 50 mg of sulfamethazine per 100 ml. These quantities of sulfathiazole are much larger than those used in the former in vivo test and show that the former activity must have been due to the small amounts of drug actually inoculated into the yolk-sac.

It was thought that, if the agent of lymphogranuloma venereum were capable of any metabolism outside the host cells, such might occur only very slowly. For this reason sulfathiazole in high concentration was again used and incubation carried out for 2½ or 3 hours at 37°C. Solvent controls showed that concentrations of solvent equal to those in the concentrations of sulfathiazole used had no virucidal action and were at best only slightly virustatic. As a further control the usual

TABLE II

DATE	DRUG	CONCENTRATION	# of eggs infected	Survival time	Control		# of infective doses used
					# of eggs infected	Survival time	
9/25/42	ST	50 mg/100 ml.	5/5	4.3 d.	4/4	4.0 d.	5,000
9/30/42	SD	50 mg/100 ml.	4/4	5.0 d.	5/5	4.9 d.	50,000
10/7/42	SM	50 mg/100 ml.	5/5	5.9 d.	4/4	5.1 d.	50,000
10/19/42	SD	125 mg/100 ml.	5/5	3.9 d.	5/5	4.3 d.	500,000
10/19/42	ST	0.5 g/100 ml.	4/4	4.1 d.			
10/19/42	ST	1 g/100 ml.	5/5	5.7 d.			
10/19/42	ST	2 g/100 ml.	4/4	6.1 d.			

amount of infected yolk-sac i.e., 500,000 infective units was incubated with 0.4 mg. per 100 ml of sulfathiazole. This mixture was centrifuged and washed as usual, but the washing was carried out with broth containing 0.4 mg per 100 ml ST and this was used for final resuspension. This inoculum, therefore, contained 6 times the amount of sulfathiazole left in the final inoculum after the manipulation of the 1 or 2 g per 100 ml sulfathiazole concentrations (See above). This latter control at 0.4 mg per 100 ml was virustatic, but was not virucidal. On the other hand, in repeated tests one solution of sulfathiazole was definitely virucidal at 2 g per 100 ml and virustatic at 1 g per 100 ml (Table III).

These results would indicate that sulfathiazole in sufficiently high concentration has a definite virucidal action. However, a second solution of sulfathiazole has failed to show any such activity in duplicate tests, and it remains to determine whether the original results are due to some chemical contamination of the ST solution. In a new experiment at present in progress with yet a third ST solution no deaths have occurred in 6 days with 2 g ST per 100 ml. All of the solvent 50% and ST 0.4 mg/100 ml controls are infected and dead.

Arsenicals: Using the *in vitro* technique outlined above under the section on sulfonamides, but with only 1 hour of incubation, many trivalent arsenical drugs have been tested for virucidal or virustatic activity. Chemical estimations of drug remaining after the three centrifugations show that this is significantly greater than in the case of the sulfonamide drugs and may amount to between 1% and 3%. This means that from 0.5% to 1.5% of the original drug concentration may be introduced with the agent into the yolk-sac. There again, however, it would appear that this amount of drug may become actually fixed to the components of the sediment.

Arsenicals tested include Clorarsen and Mapharsen, as well as certain others prepared by Dr. Egle and Dr. Doak of Baltimore, by Mr. Lott at New Brunswick, and by Dr. Christianson of Brooklyn. In all, 34 compounds have been tested. Of these, 9 have only been tested once. Of the other, 25, 17 are of very low activity with very

TABLE III

DATE	DRUG	CONCENTRATION	Final suspension	# of eggs infected	Survival time	Control		# of in- fective units used
						# of eggs infected	Survival time	
11/27/42	ST	2 g/100 ml	Broth	0/5				
	ST	1 g/100 ml	Broth	3/3	6.8 d.	5/5	4.0 d.	50,000
	ST	0.4 mg/100 ml	Broth containing 0.4 mg/100 ml	4/4	10.1 d.			
	Sol- vent	50%	Broth	5/5	5.3 d.			
	Sol- vent	25%	Broth	4/4	4.3 d.			
	12/3/42	ST	2 g/100 ml	Broth	0/4			
ST		0.7 g/100 ml	Broth	4/4	5.6 d.			
ST		0.4 mg/100 ml	Broth containing 0.4 mg/100 ml	5/5	8.5 d.	5/5	3.3 d.	500,000
Sol- vent		50%	Broth	5/5	3.8 d.			
Sol- vent		25%	Broth	4/4	4.0 d.			

little or no activity at 7.5 mg per 100 ml. The approximate concentrations of the other 8 drugs preventing death in 50% of embryos is shown in Table IV.

It is clear that the 4,4'-disulfanilamido-arsenobenzene and 4,4'-disulfanil-amido arsine-oxide are the most effective of the drugs so far tested, being approximately 3 times as good as those which are next in order of effectiveness. It should be pointed out, however, that the apparent activity of the 4,4'-disulfanilamido arsenobenzene may have been due to its conversion to the corresponding arsine oxide during or following the preparation of the test solution.

Other substances. Penicillin is virucidal at 2250 Florey units per 500,000 infective units and aspergilliac acid at 1125 R units. 500 F units of penicillin and 128 R units of aspergilliac acid are virustatic.

TABLE IV

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4289 SC	Dichlor compound of 4,4'-disulfanilamidic arsenobenzene	1.2 mg %
4289 J (434)	4,4'-disulfanilamido arsenobenzene	1.6 mg %
524	4,4'-disulfanilamido arsine-oxide	1.7 mg %
Clorarsen	-----	4.0 mg %
484	4,4'-di- (3-amino-4-hydroxy benzene sulfonamido) arsenobenzene	5.0 mg %
Mapharsen	-----	5.1 mg %
E1	4-COH <sub>2</sub> phenylarsine oxide	5.1 mg %
E4	4-NHCOCH <sub>3</sub> phenylarsine oxide	5.1 mg %

---

The virucidal action of detergents for the agent depended upon the group to which they belonged. Thus the cationic detergents MC-474, MC-507 and Emulsol 607 are virucidal at 0.5% - the lowest concentration tested. Tergitol penetrant '7', an anionic detergent, is virucidal at 0.001%, but the neutral detergents Igepal CA, Triton NE, Domal and Duponal DC are inactive even in concentrations as high as 20%. Calomel in saturated water solution was inactive against the agent.

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Chairman's Comment: General discussion pointed out that in the reports so far made, the arsenicals seemed to provide the most promising lead for further study in syphilis, gonorrhoea and lymphogranuloma, since there was a clear indication of their simultaneous effectiveness against these three diseases. Their use should be immediately extended to chancroid, and if possible to granuloma inguinale.

There were no suggestions for expansion of Dr. Rake's work by other investigators since his is the only laboratory in the country correctly equipped for this study of lymphogranuloma. It was the consensus that Dr. Rake himself should extend and amplify his own observations as rapidly as possible.

FRANK C. COMBES, M.D. AND ORLANDO CANIZARES, M.D., NEW YORK UNIVERSITY, NEW YORK

### PROPHYLAXIS OF CHANCROID INFECTION

The purpose of this report is to present the results of a study of various bactericidal and bacteristatic agents in the prophylaxis of chancroidal infections. Autoinoculations and the experimental epidermal inoculation of cultures of H. Ducreyi were used for this purpose.

The prophylactic agents used were ointments containing metallic mercury, calomel, sulfathiazole and sulfanilamide. In addition, tests were made to determine the value of soap and water locally, and sulfathiazole by mouth.

A study of autoinoculations was first pursued. This report is divided into four (4) sections:—A. The Method, B. The prophylactic agents, C. Tabulation of results, and D. Comment.

#### A. The method.

Autoinoculations were performed on the external aspect of the arms. The material used was obtained from the genital ulcers of patients inoculated. Only lesions presenting numerous H. Ducreyi were used. Autoinoculations were performed by the method of multiple punctures, a modification of the Ravaut technique, which in our hands has been found very successful. The number of autoinoculations performed on each arm varied from 2 to 4. These were done aseptically and covered with sterile gauze bandage. The ointments were rubbed on each inoculation for two minutes and covered with sterile gauze. Unabsorbed ointment was left in situ. One control was left on each arm. The period lapsing between inoculations and the application of the prophylactic, if not otherwise specified, was one hour.

The incubation period varied from 2 to 4 days. After the second day several small pustules were noticed at the point of inoculation. These were not broken to prevent secondary infection. Early positive lesions presented the appearance of large pustules containing a moderate amount of pus. This pustule when broken showed a deep ulcer. Later, lesions presented a diameter of 1 cm. or larger. The borders were undermined and soft.

#### B. The Prophylactic Agents.

1. Soap and water. The lesions were washed with liniment of soft soap (U.S.P.) using sterile gauze.

##### 2. Ointments.

(1) Sulfathiazole 5 and 10 per cent in yellow ointment (U.S.P.)

(2) Sulfathiazole 5 per cent

Calomel 15 per cent

Hydrous wool fat aa

White petrolatum

(3) Sulfathiazole 10 per cent

Cholesterolized petrolatum

(4) Mild mercurial ointment (U.S.P. XI) 30 per cent

#### C. Tabulation of Results

##### Explanation of Criteria

"Clinically positive, Ducrey positive" was applied to autoinoculations presenting the clinical appearance of a chancroid in which H. Ducreyi were found.

"Clinically positive, Ducrey negative" was applied to similar lesions in which repeated search for H. Ducreyi was unsuccessful.

"Doubtful" was applied to small erosive lesions covered with a yellowish crust more suggestive of a predermic lesion than a chancroidal one. The search for H. Ducreyi was always unsuccessful in them.

"Negative" included those in which no reaction was noted after two or more days.

TABLE I  
(Autoinoculations)

	TOTAL	NEGATIVE	DOUBTFUL	Total Neg.	Percent Neg.	Clinically Positive		Total Positive
						Ducrey Negative	Ducrey Positive	
Sulfathiazole 10%	19	11	4	15	79%	2	2	4
Sulfathiazole 5%	8	2	2	4	50%	0	4	4
Mercurial Ointment	17	0	0	0	0	7	10	17
Soap and Water	19	0	0	0	0	4	15	19
Sulfathiazole and Calomel	10	1	3	4	40%	5	1	6
Sodium Sulfathiazole in Aquafor	5	1	1	2	40%	1	2	3
Sulfathiazole and Calomel (3 hrs. later)	4	0	0	0	0	0	4	4

D. Comment.

Twenty-four sets of inoculations were made. Five of these were eliminated from this report as the control was negative. The number of slides examined in each case varied from 10 to 57. A total of 405 slides were examined from the auto-inoculations.

The "negative" and "doubtful" results were added and considered "negative" to simplify the interpretation. All clinically positive are classified as "positive" because in the great majority, H. Ducreyi were found.

A study of Table I shows that of the substances tried, sulfathiazole 10 per cent gave the best results. Mercurial ointments, and soap and water were consistently unsuccessful as prophylactics. The mixture of sulfathiazole and calomel gave poorer results than sulfathiazole alone. Sodium sulfathiazole in cholesterolized

petrolatum was less effective than sulfathiazole in petrolatum and wool fat.

The second studies, undertaken early in January, consisted of inoculation of cultured H. Ducreyi and the subsequent application at intervals of 1, 3 and 6 hours of sulfanilamide and sulfathiazole, 20 per cent, in Thompson's emulsification base.

Briefly this consisted of application of inoculum with one minute of rubbing, followed in 1, 3 and 6 hours by the application of the prophylactic by a five minute rubbing. One hundred sixty-five inoculations and 33 controls have been done. Of these only 124 are included; the other 41 having been discarded for different reasons. To date sulfathiazole, 20 per cent, and sulfanilamide, 20 per cent, have been tested.

The results obtained are presented in Table II.

T. BLE II

	Total	Negative	Percent Negative	Clinically Positive Ducrey Negative	Ducrey Positive	Total Positive
<b>Sulfathiazole 20%</b>						
1 hour after inoculation	28	12	43%	2	14	16
3 hours	20	5	25%	5	10	15
6 hours	12	2	17%	5	5	10
<b>Total:</b>	<b>60</b>	<b>19</b>	<b>32%</b>			<b>31</b>
<b>Sulfanilamide 20%</b>						
1 hour after inoculation	24	7	29%	2	15	17
3 hours after inoculation	16	3	19%	5	8	13
6 hours after inoculation	24	7	29%	3	14	17
<b>Total:</b>	<b>64</b>	<b>17</b>	<b>26%</b>			<b>47</b>
<b>Total:</b>	<b>124</b>	<b>36</b>		<b>22</b>	<b>60</b>	<b>78</b>

Comments

The results with sulfathiazole 20 percent seem to be slightly better than those obtained with sulfanilamide 20 per cent.

Sulfathiazole 20 per cent gave more satisfactory results in the application 1 hour and 3 hours after the inoculation. Sulfanilamide 20 per cent was slightly better than sulfathiazole 20 per cent when applied six hours after inoculation. This point requires further study.

Oral Prophylaxis

The value of sulfathiazole by mouth as a prophylactic against chancroid was tried in 13 patients. In each case two inoculations were performed, one on either arm.

In six patients, 2 gms. were given two hours after the inoculation and 1 gm. four hours after the first dose. In this group two patients gave negative results and the other 4 presented a clinically positive inoculation in which H. Ducreyi were found in three instances. In two patients the inoculation in one arm resulted in an ulcer, while in the other it was negative.

A second group of six patients receiving 3 gms. two hours after inoculation, 2 gms., four hours later and a third dose of 1 gm. four hours later were completely protected, the controls being positive. One patient receiving 4 gm. of sulfathiazole before the inoculation gave negative results.

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Further studies are being conducted using 5 per cent sulfathiazole and 5 per cent sulfanilamide in the emulsification base. Studies are also being pursued using these bases in autoinoculation chancroids, since in our hands pure cultures and even dilutions are too potent and do not represent actual conditions.

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Chairman's Comment: Discussion of Greenblatt's and of Combes and Canizares reports hinged around the differences in technic employed, the as yet inadequate number of cases studied to provide statistically convincing data, and the desirability of studying the arsenical drugs as promptly as possible. These points are further discussed in the reports of sub-group chairman (see below).

Nevertheless, this work, as so far prosecuted, has demonstrated that neither soap and water or calomel ointment is effective in prevention of chancroid and that present Army and Navy prophylactic systems are worthless in this respect.

# **Continued on Next Fiche!**

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ROBERT B. GREENGLASS, UNIVERSITY OF CHICAGO

THE PROPHYLAXIS OF CHANCROIDAL INFECTION

PART I

1. Chancroid ulcers were produced experimentally by inoculation of scarified areas with recently isolated virulent strains of *Haemophilus ducreyi*. This study is concerned with the results of 28 series of inoculations in 170 scarified areas performed on 19 volunteers. Stock cultures, maintained in the laboratory and transferred at frequent intervals for more than 3 years proved incapable of producing the disease experimentally. One such strain was previously shown to have been virulent.

2. In 24 control inoculations, chancroid lesions developed in all instances but one. The one failure must be considered as an error in technique, for in the same patient typical lesions resulted in several of the inoculated areas in spite of the medication that was applied.

3. The prophylactic use of castile soap and water, surgical soap solution, calomel ointment, silver picrate jelly, and a mercurial antiseptic proved useless in every instance in which such medication was employed.

4. Sulfathiazole administered orally following inoculation, before inoculation, as well as before and after inoculation prevented the production of experimental chancroid. Oral sulfathiazole administration, however, proved ineffective in preventing chancroid lesions if, after cessation of therapy, 3 to 5 days were allowed to elapse before the experimental inoculations were performed.

5. The application of anti-bacterial agents in the form of sterile powders such as sulfathiazole, sulfanilamide, sulfadiazine, and sulfasuxidine, sprinkled over the inoculated area, proved effective. When tyrothricin was used similarly, it did not prevent the occurrence of a chancroid lesion.

6. Five per cent sulfathiazole in a water miscible base proved useful in the prophylaxis of chancroid disease in 5 of the 12 inoculations. When a mixture of 5 per cent sulfathiazole, 5 per cent sulfanilamide, 2 per cent urea, and 26 per cent cod-liver oil in a water miscible base was used, 3 of the 6 inoculations ended in typical chancroidal lesions. When 10 per cent sulfathiazole in a water miscible base was employed, lesions developed in 4 of 8 inoculations. Twenty-five per cent sulfathiazole in a water miscible base was used in one instance and proved partially successful. Of the 27 inoculations in this series in which sulfathiazole ointments were used, prophylaxis was successful in 12, partially successful in 4, and failed in 11 instances.

7. The addition of sulfathiazole or one of the sulfonamides in sufficient concentration to calomel ointment so as to result in a mixture containing at least 20 to 25 per cent of the sulfonamide proved promising as an effective prophylactic agent. When a mixture of 20 to 33 per cent of a sulfonamide and 25 to 33 per cent of calomel was employed, successful prophylaxis resulted in 25 of the 34 inoculations. Since the incorporation of a sulfonamide to the calomel prophylactic tube now generally in use makes it effective in the prophylaxis of chancroid it is hoped that this addition will not minimize the effectiveness of the calomel in the prevention of syphilis. This point remains to be proved.

8. Further work is necessary to ascertain the ideal base for the most effective sulfonamide in combination with calomel in the prophylaxis of chancroid disease.

## PART II

### Experiment No. 1

The present strain of Ducey bacillus being used in the experimental production of chancroid disease has been found to be too virulent since a large proportion of takes were obtained in spite of chemical prophylaxis with the various sulfonamide agents. It was decided to dilute cultures 1:2, 1:5, and 1:10. Eleven series of inoculations were done on 8 patients. In each series, the patient received 2 sets of inoculations with each of the 3 dilutions, i.e. six inoculations. To one of each of these sets, a mixture of 20 per cent sulfathiazole and 33 per cent calomel prepared in a base of sulfonated, hydrogenated castor oil and water, was applied one hour after inoculation. The above medication was applied in all, but in 3 instances 20 per cent sulfadiazine was substituted for the sulfathiazole. Analysis of the results yielded the following information: The inoculations with 1:2 dilution yielded positive takes in 10 of 11 instances, and prophylaxis was successful in 10 of 11 medicated inoculations. The inoculations with 1:5 dilution yielded positive takes in 9 of 11 instances, and prophylaxis was successful in all 11 medicated inoculations. The inoculations with 1:10 dilution yielded positive takes in 8 of 11 instances, and prophylaxis was successful in 9 of 11 medicated inoculations.

### Summary of Experiment 1

Of 33 inoculations with the various dilutions, positive takes were obtained in 27 instances. Although there was a greater number of failures (3 of 11) with control inoculations with the weakest dilution (1:10), there was also the greatest number of prophylactic failures with this dilution (2 of 11). Of 33 inoculated areas to which chemical prophylaxis was applied, successful prophylaxis was obtained in 30 instances.

### Experiment No. 2

Observations on the virulence of one recent strain and 4 old strains of Ducey bacillus were made. All strains showed active growth although in 2 of the old strains, the growth of bacteria was not so luxuriant as in the 2 others or in the recent strain. Five patients were inoculated with each of the 5 cultures. Takes were obtained in all five cases with a 1:2 dilution of the recent strain (8 months old). Failures were encountered in each instance with each of the 4 old strains employed. The old cultures were passage strains of over 4 years' duration. This experiment would tend to prove that repeated passage of strains in the laboratory decreases the virulence of the organism. One of these strains was used successfully in the experimental production of chancroid disease in 1937. Failure to produce the disease was encountered on 4 separate trials in 1942.

### Summary of Experiment 2

Repeated passage of Homophilus duceyi in the laboratory tends to decrease the virulence of the organism for man.

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Chairman's Comment:- The reports of Greenblatt and of Combes and Canegares were discussed together and comment will be found after the letter.

Charles M. Carpenter, Helen Ackerman, and Herbert E. Stokinger

THE EFFECT OF SURFACE-ACTIVE AGENTS ON NEISSERIA GONORRHOEAE  
AND TREPONEMA PALLIDUM IN VITRO\*

A comparison was made of the bactericidal activity on Neisseria gonorrhoeae and Treponema pallidum of recently developed chemical agents for possible use as venereal disease prophylactics. The substances studied comprised; (1) neutral, anionic, and cationic surface active agents; (2) mercurial and arsenical compounds; (3) sulfonamide compounds; (4) currently employed prophylactic agents; and (5) penicillin and tyrotracin.

Tests of the bactericidal activity against the gonococcus were carried out as follows. The chemical agents were dispersed in a tragacanth-water or tragacanth-phosphate buffer medium at approximately pH 7 at various concentrations indicated in the accompanying tables.

The concentration of tragacanth was 4.5 per cent. The preparation was placed in a well 1.5 cm. in diameter made in a "chocolate" agar plate after inoculation of the surface with the gonococcus. The plates were incubated at 36° C. for 48 hours. The radius in millimeters of the zone of inhibition of growth surrounding the well, was the measure of bactericidal activity for the agent.

The loss of motility was employed as a test for the activity of the compounds against Treponema pallidum. Equal quantities of fluid expressed from syphilomas in rabbits' testes and a solution of the chemical agent at approximately pH 7 were combined. The mixture contained at least three or four spirochetes per field. The final concentration of the preparation is designated in the tables. Observations on motility were made by darkfield illumination immediately after exposure of the spirochetes to the surface active agents, ten minutes later, and in some instances after one hour of exposure.

RESULTS

The results of the tests are summarized in the accompanying tables. Of all of the agents tested, ethyl mercuric phosphate exhibited the most marked bactericidal action on the gonococcus, a concentration of 0.01 per cent producing an inhibitory zone extending 23 mm. from the periphery of the well. The mercurial compounds, in the order of decreasing effectiveness, were aliphatic > aromatic > inorganic. A marked decrease in the activity of calomel was observed when it was incorporated in a fatty vehicle. Sulfathiazole produced an inhibitory zone equal to that produced by ethyl mercuric phosphate, but required a concentration fifty times greater. The arsenical compounds were less effective than sulfathiazole in the concentration employed. (Table I) The surface active agents as a group were less bactericidal for the gonococcus than the preparations presented in table I. No correlation between chemical structure and activity could be observed among the most effective of this group. (Tables II and III).

The activity of ethyl mercuric phosphate was not decreased by combination with certain of the better surface active agents. (Table IV).

∴ The surface active agents, on the whole, immobilized Treponema pallidum on contact. Several of the superior compounds have been classified according to their

action against both Neisseria gonorrhoeae and Treponema pallidum. Of the preparations tested, only a few were effective against both organisms. (Table V).

#### DISCUSSION

In tests for determining bactericidal activity, the choice of method is important. The in vitro procedure adopted for these studies was simple and rapid and gave reproducible results. The variation for the greatest radius of the zone of inhibition was  $\pm$  1.5 mm. A series of concentrations of a given compound under the test conditions, gave a radii of inhibitory zones proportional to the concentration of the compounds. Moreover, for a series of compounds of similar structure, such as the sulfonamides, the gradation in zones of inhibition was consistent with the therapeutic activity of the compound in vivo. A comparison of the activity of several compounds in broth and on "chocolate" agar has given uniform results. Exceptions, however, were noted in the case of cationic detergents bearing the cetyl group.

The results reported herein indicated that surface active agents, regardless of diverse chemical structure, were active against Treponema pallidum in vitro but with few exceptions, relatively inactive against the gonococcus. On the other hand, the compounds of heavy metals and of sulfonamides exerted marked activity against the gonococcus but failed to render Treponema pallidum non-motile.

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Chairman's Comment: General discussion brought out the facts that (a) the dilutions reported in the accompanying tables are not limiting dilutions; and the data given are therefore relative rather than absolute, (b) the bacteriologic technique herewith employed differs from the in vitro techniques of Miller and of Hill, and is open to certain serious bacteriologic objections. It was suggested that the three laboratories employing in vitro tests of gonococidal activity of drugs agree on a standard method for future use.

TABLE I  
INHIBITION OF THE GROWTH OF THE GONOCOCCUS IN VITRO  
BY HEAVY METAL PREPARATIONS, SULFATHIAZOLE AND PENICILLIN

PREPARATION	CONCENTRATION	RADIUS OF ZONE OF "NO GROWTH"
Ethyl mercuric phosphate	0.01	23
Penicillin *	0.10	23
Sulfathiazole	0.50	23
Merthiolate	0.01	20
Phenyl mercuric nitrate	0.01	17
Phenyl mercuric sulfonamide	0.50	15
Napharsol	0.01	14
Neocarsphenamine	0.01	14
Mercurous chloride (calomel)	0.01	13
Arsphenamine diarsmol	0.01	12
Calomel ointment (Squibb NFVI)	100.00	8

\* 75 Florey units per mg.

TABLE II  
INHIBITION OF GROWTH OF THE GONOCOCCUS IN VITRO  
BY SURFACE ACTIVE AGENTS IN A CONCENTRATION OF ONE PER CENT

PREPARATION TRADE NAME	RADIUS OF ZONE OF "NO GROWTH"	CHEMICAL NATURE OF PREPARATION
1. Dowieide A	12	Sodium orthophenyl phenate
2. Mergotino	10	Sodium alkyl naphthalene sulfonate
3. Aerosol OS	9	Alkyl aryl sulfonate
4. Aerosol OT 100%	7	Diocetyl ester of sodium sulfosuccinic acid
5. Dry Santomorse	6	Alkyl aryl sulfonate
6. Neopon SS	6	Sodium abietate sulfonate
7. Duponol PC	4	Fatty alcohol sulfate
8. Cresket 300 Dry	4	Monobutyl diphenyl sodium monosulfonate
9. Sorbitol Derivative	4	Sorbitol ricinoleate
10. Creskolene 400 Dry	3	Libutyl phenyl phenol sodium disulfonate
11. Aerosol OTC	3	Sodium sulfosuccinic acid
12. Alkanol B	3	Sodium alkyl naphthalene sulfonate
13. Duponol ME	3	Aliphatic alcohol sulfate
14. Aquasorex F	3	
15. Tergitol Penetrant	3	Sodium salt of higher secondary alkyl sulfate
16. Triton 720	3	Sulfonated ether
17. Dreft	2	Sodium lauryl sulfate
18. Tergitol Penetrant 4T	2	Amine salt of higher secondary alkyl sulfate
19. Metanol	2	Modified sulfated aliphatic acid ester
20. Virifoam A	2	
21. Triton W-30	2	Sulfated aromatic ether alcohol
22. CCCC Soapitol G. A. R.	1	Sulfonate of higher alcohol.
23. Tegasept B	1	Benzyl p-hydroxy benzoate
24. Cerbowax 4000	0	

TABLE III  
INHIBITION OF GROWTH OF THE BACILLUS IN VITRO BY CATIONIC  
SURFACE ACTIVE AGENTS IN A CONCENTRATION OF 0.5 PER CENT

PREPARATION	RADIUS OF ZONE OF "NO GROWTH" MM.
B-amoxyethyl diethyl benzyl ammonium chloride	15.0
Cetyl pyridinium chloride	4.5
Cetyl diethyl morpholinium iodide	2.0
●Cetyl diethyl B-chloroethoxy ethyl ammonium chloride	2.0
●Cetyl diethyl B-hydroxyethyl ammonium chloride	1.5
●Cetyl din-propyl B-hydroxyethyl ammonium chloride	1.5
●Cetyl B-hydroxy ethyl piperidinium chloride	1.5
●Cetyl diethyl B-hydroxy ethyl ammonium bromide	1.5
●Cetyl B-hydroxyethyl morpholinium iodide	1.0
●Cetyl din-butyl B-hydroxyethyl ammonium chloride	1.0
●Cetyl dimethyl B-chloroethoxy ethyl ammonium chloride	1.0
Cetyl dimethyl benzyl ammonium chloride	0.5
●Cetyl dimethyl B-hydroxyethyl ammonium chloride	0.5
●Cetyl dimethyl butyl ammonium chloride	0.5
●Cetyl dimethyl p-nitrophenyl ammonium chloride	0

● Synthesized by Ortho Products, Inc., Linden, New Jersey

TABLE IV  
INHIBITION OF GROWTH OF THE BACILLUS IN VITRO OF  
ETHYL MERCURIC PHOSPHATE IN COMBINATION WITH SURFACE ACTIVE AGENTS

PREPARATION	RADIUS OF ZONE OF "NO GROWTH" MM.
Ethyl Mercuric Phosphate, Luponol 1M	25
Ethyl Mercuric Phosphate, Triton W 30	24
Ethyl Mercuric Phosphate, Zephiran	23
Ethyl Mercuric Phosphate, Aerosol OT 100	23
Ethyl Mercuric Phosphate, Dowicide No. 2	24
Ethyl Mercuric Phosphate, B amoxyethyl diethyl-benzyl ammonium chloride	24

Composition of Preparations:

Ethyl mercuric phosphate	0.01%
Surface active agent	1.00
Gum tragacanth	4.50
Water	94.49

COMPARATIVE IN VITRO EFFECTIVENESS OF VARIOUS PREPARATIONS AGAINST  
THE VIABILITY OF N. GONORRHOEA AND THE MOTILITY OF T. PALLIDUM

PREPARATION	ACTIVITY AGAINST	
	N. GONORRHOEA	T. PALLIDUM
	conc.	conc. *
Aerosol Ma	+ 1.0	+ 0.5
Aerosol OT 100	+ 1.0	+ 0.5
Dowicide A	+ 1.0	+ 0.5
Duponol MEW	+ 1.0	+ 0.1
Zephiran ("Roccal")	+ 1.0	+ 0.1
B-amoxyethyl diethyl benzyl ammonium chloride	+ 1.0	- 0.5
Ethyl mercuric phosphate	+ 0.001	- 0.15
Penicillin	+ 0.1	- 0.5
Cetyl di-n-butyl B-hydroxyethyl ammonium chloride	- 0.5	+ 1.0
Cetyl diethyl B-hydroxyethyl ammonium chloride	- 0.5	+ 1.0
Triton W-30	- 1.0	+ 0.5
Tyrothricin (J & J Jelly)	- 0.1	+ 0.15
Dreft	- 1.0	+ 0.05
Antipyrine	- 1.0	- 0.5
Tegasept B	- 1.0	- 0.5

- + = Bactericidal for N. gonorrhoeae - radius of zone of "no growth" greater than 5 mm. as tested by the well method; or cessation of motility of T. pallidum after contact with preparation.
- = Slight or no bactericidal activity against N. gonorrhoeae - radius of zone of "no growth" less than 5 mm.; or no inhibition of motility of T. pallidum after contact with preparation for 10 minutes.
- These are not limiting concentrations.

MARVIN R. THOMPSON, WARNER INSTITUTE

Vehicles for Topical Chemotherapeutic Preparations

The probability of discovering a drug which, upon oral administration, will afford adequate protection from venereal infection and yet prove harmless is extremely remote. Certain of the sulfonamides, mercurials and bismuth compounds have been studied as oral prophylactics, but even if they proved effective in preventing the several types of venereal infection, the systemic toxicity and side actions constitute too great a risk in mass use for such a purpose. The sound approach to the problem would therefore be to decide from the outset that the prophylactic measure must involve local treatment--upon intraurethral and exterior surfaces--involving both mucous and skin surfaces.

This being true, the chemoprophylactic agent or agents must be carried in a suitable vehicle. The importance of the vehicle is critical. The best chemoprophylactic agents that are ultimately worked out by our group can be rendered practically inert and worthless by their incorporation into the wrong type of vehicle. The selection of the vehicle cannot be random. Each new chemoprophylactic substance studied must be suitably incorporated in a vehicle specially designed to permit its optimal performance under practical and specific conditions of use. Mixtures constitute a still more complex vehicle problem.

In vitro and in vivo methods have now been developed to such a point that their application can be made to evaluate critically the suitability of any topical application for its intended specific purpose.

Physical and chemical specifications and methods of checking these specifications have been worked out in such a manner as to insure satisfactory performance of such topical applications under practical conditions of use wherever our armed forces may be.

Future efforts should be directed toward the careful continued testing of certain sulfonamide, mercurial, arsenical, silver and bismuth compounds for their relative effectiveness against the infective agents of the four venereal diseases involved. The probability that the most generally effective product will involve more than one chemoprophylactic agent is being anticipated by studies already in progress. It is obviously desirable from practical considerations to have the entire prophylaxis embraced in one single product, rather than in two or more separate products as now used in the armed forces. Even though this will necessitate a vehicle which will insure satisfactory effectiveness of the chemoprophylactic agents when applied to both skin and mucous surfaces (which obviously represent two different sets of physiochemical conditions) reasonable assurance can be given at this early date that such is entirely feasible.

A series of topical applications containing a variety of combinations of sulfonamide, mercurial, arsenical, bismuth, and silver compounds have been prepared in a number of types of vehicles and are being studied from the standpoint of compatibility, stability, interference of one agent with the behavior of other agents in the mixture, absorption and diffusion characteristics, etc. All of such information will be essential when we are ready to attempt to reduce our experimental studies to practice, and obviously, stability observations over a period as long as possible, with a variety of combinations of chemoprophylactic agents and vehicles will be very necessary and helpful. The question of containers is likewise extremely important and is receiving extensive consideration.

All members of the Sub-Committee should be encouraged to submit all new chemoprophylactic agents of promise, as soon as they have shown reasonable effectiveness in appropriate tests, to Dr. J. L. Moore, Chairman of the Sub-Committee, so that he may place them in the hands of Dr. H. O. Calvery, Chairman of the Sub-Group on Vehicles. Only in this way can the study be systematically expedited in such a manner as to make improved venereal prophylaxis available to our armed forces at the earliest possible moment.

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Chairman's Comment:-Dr. Thompson was unfortunately prevented from presenting this report in person because of a prior engagement. The report was not therefore discussed at the Conference.

The Chairman (Dr. J. L. Moore) will welcome written comments from the conferees, which can then be circulated to the group.

Herbert O. Calvery,  
Chief, Division of Pharmacology,  
Food & Drug Admin., Federal Security Agency

Principal Problem: Influence of Surface Active Agents on Absorption of Therapeutically Active Components from Different Ointment Bases.

PROGRAM AND PERSONNEL

- I. General classes of substances to be studied:
  - A. Surface active agents;
  - B. Components of bases not previously studied;
  - C. Finished products.
  
- II. Pharmacological and Toxicological Studies: (J. H. Draize, B. J. Vos, Jr., G. Woodard, and P. M. Jenner).
  - A. Skin, mucous membrane and conjunctival membrane irritation, and supply animal tissues and excreta to analysts for chemical analysis to determine relative absorption of each therapeutic agent from different types of bases. Both skin and mucous membranes to be used as absorption surfaces. Animals to be used: rabbits, guinea pigs and dogs.
  
  - B. Proposed Tests for Local Irritation:
    1. Conjunctival sac method using rabbits' eyes. Different types of injury given a numerical score depending on degree of severity and parts of the eye involved.
    2. Intracutaneous injection into skin of guinea pig.
    3. Mucous membrane irritation using vagina and penis of rabbit, guinea pig (?) and dog.
    4. Topical application to skin: The amount of irritation is scored by assigning numerical values to the degree of erythema and edema produced by the various agents. The system of scoring used gives a maximum value of 8 wherein there is maximum redness and eschar formation along with an edema of greater than 2 mm.
  
  - C. Sensitization: Intracutaneous injection into skin of guinea pigs and possibly rabbits by Landsteiner's technique.
  
  - D. Systemic Toxicity: If some of these substances are readily absorbed their systemic effects should be known. Methods of application for both acute and subacute studies: (a) skin; (b) oral; (c) intravenous; and (d) subcutaneous. Relative mortality in rats, mice, guinea pigs and rabbits.
  
- III. Relative absorption of mercurous chloride (Calomel) from different types of ointments; relative concentration of mercury in blood and tissues compared to histological picture; mercury analysis made by use of the dithizone method. (L. P. Laug, D. Hughes, and H. U. Anderson).

Up to the present time 3 ointments containing mercury have been applied to the skin of rabbits for the purpose of determining mercury in the blood and urine. The inunction time was 5 minutes, the area 3 x 5 inches, the amount of ointments used was sufficient to furnish 300 milligrams per kilogram of Calomel. The ointments used were Army Calomel Ointment, Navy Calomel Ointment and the Calomel Ointment prepared by Dr. Thompson. Particle size of the Calomel in each of these ointments ranged in diameter from 3 to 33 micra. Samples of blood and urine were taken before application of the ointment and at the following periods subsequent to the application: 6 hours, 30 hours, 54 hours, 78 hours. So far the quantities obtained in the blood and urine at any of these periods of time are not sufficiently different from the control to be able to say whether there has been absorption into the blood stream from the site of application. Longer inunction times are being studied and other areas of application in order to try to determine whether there are different amounts of mercury being absorbed from different types of bases. Other types of ointment bases will also be used.

- IV. Chemical Investigations Other than Mercury Analyses: (E. S. Shupe, S. M. Berman, C. D. Wright and K. K. Ofner).
- A. Melting point, stability, compatibility of mixtures, temperature effects, stability of final product.  
The Navy ointment is stable at room temperature and below but at 50° C within 12 hours there is almost complete separation of the Calomel from the melted ointment base. Army ointment is stable but there is rapid separation of the Calomel from the melted base at 50°C. Warner ointment was held at -15° for 8 hours and a few ice crystals seemed to form but no significant change was noted in the emulsion after warming it again to room temperature. At 50° for 8 hours there is small separation of the aqueous phase. This amounted to about 6% of the total ointment. However, there was no noticeable settling of the Calomel from this base. Other Warner bases studied reacted similarly to the one mentioned above. In three commercial Calomel ointments particle size of one was 3 to 60 micra in diameter; another 1 to 20; and the other 3 to 40.
  - B. Necessary characterizations and purification of surface active agents.
  - C. Arsenic analyses.  
So far Mr. Berman has had considerable difficulty in getting reagents which are sufficiently free of arsenic not to give a blank which is too high to properly evaluate the absorption of small quantities of arsenic through the skin.
  - D. Sulfonamide analyses.
  - E. Distribution and concentrations in tissues, blood and urine.
  - F. Latent concentration in area of application.
  - G. Rate of absorption varying: time, area, wetting agent and type of base.
- V. Gross and microscopic examination of tissues after biopsy and at death of animals. Morphological changes in blood. (A. A. Nelson and C. C. Boone).

PROGRESS REPORTS

IRRITATION STUDIES ON WETTING AGENTS AND GLYCOLS

John H. Draizo

Albino rabbits of mixed sexes weighing 2.5 - 3.5 kilograms were prepared by clipping the skin free of hair 24 hours prior to exposure. Patches consisting of 2 layers of gauze were cut exactly 1 inch square, were held on the subject by strips of adhesive tape. The patches were saturated with 0.5 ml. of the test solution and then covered by rubberized cloth to prevent excessive evaporation. The area chosen for exposure is the upper flank, a few centimeters off the spinal column. Each rabbit is exposed to four patches at one time so spaced as to be approximately 4 inches apart. Each preparation was tested on 6 subjects (3 intact, 3 abraded skin exposures). The animal is immobilized in a special holder fashioned after a head and hip stock, and rests comfortably on its belly. Patches are removed after 24 hours contact with the skin. The evaluation of the reactions is then made using a scoring system evaluating the erythema and edema.

The various wetting agents indicated in Table I gave values as summarized. The third column is the average or composite reading for six animals. The skin was abraded by making 4 epidermal abrasions (two at right angles to the other two) in the area of the patch.

TABLE I

Irritation from Wetting Agents, 10% Aqueous Solutions

Compound	Intact Skin	Abraded Skin	Average of Six Subjects
Clay Deflocculant #2	0	0	0
Triton 720	0	0.33	0.17
Modified Sorbitan Monolaurate	0	0.67	0.20
Tergitol OS	0.67	0.33	0.50
Supergal TE	0.33	1.67	1.0
Triton NE	0.67	1.33	1.0
Araskap 100	2.0	2.0	2.17
Igepon T	2.3	2.3	2.3
Intramino DX	2.0	3.67	2.83
Alkanol WXN	2.33	4.0	3.0
Duponol C	3.0	4.0	3.5
Aerosol OT	4.33	6.0	5.15
Aerosol OS	6.0	4.67	5.2
Nacconol NRSF	6.3	6.0	6.15
Sentomorse D	5.33	7.0	6.17
Phomorol	7.33	7.0	7.17
Roccal	6.0	6.67	7.33

As a rule, all injuries scoring less than 2 points are completely healed and gave a score of zero at the end of 72 hours. Consequently all agents (10% aqueous) which gave a reading of 2 or more at 24 hours, were repeated in 2% aqueous concentrations. These results are given in Table II.

TABLE II

Irritation from Wetting Agents 2% Aqueous Solutions

Compound	Intact Skin	abraded Skin	Average for Six Subjects
Intramine DX	0	1.0	0.5
Aroskap 100	0.67	0.33	0.5
Alkanol WEN	0.33	1.67	1.0
Santomerse D	0.67	1.67	1.17
Igepon T	1.0	1.33	1.17
Aerosol OS	2.33	1.33	1.83
Nacconol NRSF	1.33	2.67	2.0
Phermerol	2.33	1.67	2.0
Aerosol OT	3.67	1.67	2.67
Zephiran Chloride	4.0	4.0	4.0
Roccal	3.33	5.0	4.17
Duponol C	3.0	5.67	4.33

Glycerine and 4 glycols were tested similarly, and gave the following results:

TABLE III

Irritation from Glycerol and Glycols --- (undiluted)

Compound	Intact Skin	abraded Skin	Average for Six Subjects
Glycerine	0	0.5	0.2
Diethylene Glycol	1.0	1.33	1.2
Triethylene Glycol	1.0	1.33	1.2
Ethylene Glycol	1.0	2.0	1.5
Propylene Glycol	1.33	4.0	2.4

Since the rabbit skin, in general, is more sensitive than the human, it is quite probable that all preparations not exceeding a score of approximately 2 would be well tolerated. This would permit the use of 10% aqueous solutions of those agents in Table I down to Igepon T. In 2% solutions it would permit the use of agents listed above Aerosol OT.

It is interesting to note that a number of these agents are more irritating to intact than to scarified skin.

Mucous Membrane Irritation Tests

Bert J. Vos, Jr.

- I. Glycerine, Propylene Glycol and Ethylene Glycol.  
Concentrations up to 15% W/V in water produced no detectable irritation when applied to:
- Rabbit's conjunctiva.
  - Rabbit's penis.
  - Guinea pig's penis.
- II. Surface Active Agents:
- Applied to rabbit's conjunctiva in dose of 0.1 cc. they fall into three broad groups:
    - No corneal damage at concentrations as high as 10%. Occasionally some conjunctival irritation, but this disappears in 24 hours.
      - Igepon T
      - Modified Sorbitan Monolaurate
      - Intramine DX
      - Triton 720
      - Supergol TB
    - Intermediate. Corneal damage at 10% concentration. No marked effects after 24 hours with 2%.
      - Tergitol OB
      - Duponol C
      - Alkanol WKN
      - Triton NE
    - Very irritating. Corneal damage from 2%.
      - Aerosol OS
      - Aerosol OT
      - Nacconol NRSF
      - Roccal
  - Applied to rabbit's penis in excess.
    - Nonirritating even at 10% concentration.
      - Triton NE
      - Supergol TB
      - Triton 720
      - Modified Sorbitan Monolaurate
      - Intramine DX
      - Clay Deflocculant No. 2
    - Moderate Irritation at 10%

Duponol C	Aerosol OS
Nacconol NRSF	Santomorse
Aerosol OT	Igepon T
Areskap	
    - Marked irritation and edema at 10%
      - Roccal
      - Zephiran
      - Phomerol

**Additional Remarks:**

Genital mucosa of male guinea pig is a considerably less delicate indicator of irritant action than that of the rabbit.

The response of the rabbit's eye permits more accurate measurement than the rabbit's penis because: (1) it is more sensitive to mild irritation; (2) the other eye can always be used as a control; (3) there are more features on which to base a score.

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Skin Absorption of Sulfathiazole in Rabbits

Geoffrey Woodard, Ruth Ofner and Paul Jenner

There were available for study five ointments containing 20% sulfathiazole as follows:

<u>Ointment Designation</u>	<u>Source</u>	<u>Contents</u>
1.	Warner Institut	Special base with micronized drug.
2.	Shupe 2-20	83% propylone glycol base.
3.	Shupe	Warner base + 1% Dupanol C
4.	Shupe	Zephiran - cold cream base
5.	Shupe	O/W Emulsion, 1% Dupanol C (Duemling)

The first four rabbits were used to determine the optimum time for taking blood and urine samples with reference to the peak level of sulfathiazole present.

The remaining rabbits were used to determine in a preliminary way, the effect of increased dosage, and the effect of the ointment base.

In each case, the rabbit was clipped with the electric clippers the evening before the experiment. Blood was taken from the ear vein. Following is a table of the blood level found in milligrams per cent.

**Discussion:**

Although the number of animals appears small, it seems that the following observations may be made:

1. Sulfathiazole is rapidly but poorly absorbed through the intact skin, sufficient to maintain a blood level from .4 to .8 mg.% for several hours with an application of 1 to 3 gm./kg. of a 20% ointment.
2. The application of 3.0 gm./kg. of ointment rather than 1.5 gm./kg. increases blood level. However, this represents a huge excess of ointment on the animal.
3. The bases tested all seemed about the same in influencing sulfathiazole absorption, with base #5 being perhaps the poorest. This base was also the most difficult to apply to the animals.
4. The peak of the blood level seems to occur before 5 hours after application since the blood level at 5 hours is the same or lower than at three hours.
5. Considerable quantities are excreted in the urine but additional work must be done to determine the value of these determinations.

Total Blood Sulfathiazole Mg.%

Rabbit No.	Ointment No.	Application Area	Dose GM/KG	Hours After Application Time of Blood Sample						
				2	3	4	5	6	8	24
1	1	100 cm. <sup>2</sup>	1.0			-		.3	.2	-
2	1	"	1.0			.8		.3	.2	-
3	1	"	1.0	.66		.64		.81		.8
4	1	"	1.0	.73		.81		.71		.5
5	2	150 cm. <sup>2</sup>	1.5		.48		.36			.38
6	2	"	3.0		.71		.60			animal dead
7	3	"	1.5		.54		.36			.44
8	3	"	3.0		.60		.41			.54
9	4	"	1.5		Lost		.38			.44
10	4	"	3.0		.54		.46			.67
11	5	"	1.5		.50		.35			.46
12	5	"	3.0		.42		.44			.33

• Note: These determinations were made against distilled water as a blank so that they are about 20% high compared with the other determinations.

Method

Determination of the sulfathiazole in the blood and urine by Marshall's method (J.B.C. 128 537 (1939) using CCl<sub>3</sub> COOH as the deproteinizing agent and N-(1-naphthyl) ethylenediamine .2% HCL as the coupling agent.

The colors were read in the spectrophotometer at 540 m/μ in the 10 cm. tube. Differences of 0.05 microgram/cc. could readily be detected down to a minimum concentration of 0.05 microgram/cc. corresponding to approximately 0.1 mg.% in the blood.

Unknowns were compared with a standard curve prepared with Merck Sulfathiazole.

1:20 dilutions were made on blood samples.

1:40 dilutions were made on urine samples.

All determinations represent total sulfathiazole (free + combined).

Blanks for each determination were taken from the filtrate for that determination.

Cooper, Gross, and Lewis. Brit. Med. J. I 456 (1941) report that hemolysis with saponin in 1:20 dilution of blood leads to a 10 - 20% loss of sulfathiazole, so that the figures probably represent 80 - 90% of the sulfathiazole present.

Lieut. Com. A. J. Polyzac, M. C., U. S. N. R.

Prophylaxis by Electrophoresis

I regret that the investigations on the use of electrophoresis in chemical venereal prophylaxis are not sufficiently advanced at this time to permit definite conclusions.

Much consideration has been given to the relative antiseptic value of different prophylactics. As much attention needs to be given to the methods of application of these prophylactics. The destruction of organisms responsible for the venereal diseases in the genital tissues is hampered by folds and recesses in the tissue which protect them from contact with antiseptics. In the case of the treponeme, its active invasive capacity removes it rapidly from the action of topically applied antiseptics. Something more than the capacity to destroy organisms is required of antiseptics; positive means must be provided to insure that they reach the organisms both in the recesses of the genital tissues and beneath the surface epithelium.

Under present methods of chemical venereal prophylaxis, some effort is made to provide this deeper action by means of massage of calomel ointment into the genital tissues and by the retention of protargol or similar solution in the urethra for sufficient time to permit penetration of the antiseptic. But these are individually variable and uncertain procedures.

One means of facilitating the penetration of antiseptics without dependence on the individual is through their combination with certain wetting agents which bring the antiseptic into more thorough contact with the surface tissues and which increase penetration. But, if added to this, an electric current is applied, a more positive and controllable force is brought into action to insure this penetration. Then, not only are the surface organisms contacted by the antiseptic, but the deeper invading spirochete is reached as well. By introducing a cotton anterior end of the urethra, the urethra is maintained open to the action of the antiseptic and prophylaxis of this important mucous surface is assured during the application of the current. The degree of penetration obtainable will vary with the antiseptic salt used, the type of wetting agent employed and the concentration of these substances. The electric potential employed and the duration of the prophylactic treatment will likewise affect the concentration and penetration of the antiseptic salt. These factors are under investigation to determine the maximum depth of the spirocheticidal action obtainable with a minimum of irritation to the tissues.

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Chairman's Comments:- There was no general discussion of this procedure.

General Summary of Accomplishments to Date

Syphilis:- Calomel ointment has been shown to be efficacious in rabbits in doses analagous to those used in man; its effect is both local and systemic. More work needs to be done on (1) the effect of particle size; (2) the inhibitory effect if any of combined sulfonamides; (3) improved vehicles.

Arsenicals locally applied are likewise of value, but work has not yet progressed far enough to determine the optimum preparation from the standpoints of stability, local and systemic toxicity, and vehicles. This work should be pushed (see below).

Gonorrhoea:- Apparent progress has been made in establishing persistent infections (for at least 14 days) if not actual gonococcal disease on the genital mucosa of mice. This work should be pushed and expanded into an additional laboratory for confirmation, since if successful it offers promise of a laboratory animal available for testing local prophylactic agents.

Sulfonamides locally applied in patients with acute gonorrhoeal urethritis show some evidence of curative effect in a small number of cases. If this is confirmed the method of study should provide a lead as to their prophylactic effect.

Various arsenicals have been found to be actively gonococidal in vitro. A search for the most active of these should be continued.

In vitro studies of gonococidal substances are not as yet standardized, and can serve only as rough screen tests.

Human experimentation is possible with the approval of C M R- O S R D; and should be pushed as rapidly as possible.

Lymphogranuloma:- Of the various agents studied, the arsenicals are as a group the most efficacious in preventing infection in the chick embryo.

Chancroid:- The inefficacy of soap and water and of calomel ointment has been demonstrated.

Sulfonamides orally administered will protect.

Sulfonamides locally applied will also protect in some cases, but studies in this respect are as yet incomplete as to the optimum drug, concentration of drug, inhibiting effect if any of added calomel, and vehicles.

Arsenicals have not as yet been studied, but should be promptly.

Granulomas inguinale:- No information as yet available.

Arsenicals:- Since evidence has been provided that these compounds included in the group of amide substituted phenylarsinoxides may be simultaneously effective against syphilis, gonorrhoea and lymphogranuloma, their effectiveness in chancroid should at once be studied. Final efforts should be centered on those one, two or three compounds which are stable, relatively non-toxic locally and systemically (especially the former) and of greatest over-all activity against several diseases at once.

Surface active agents:- Preliminary study indicates that certain of these are both troponocidal and gonococidal. These studies should be continued in order to determine which substances do and do not possess these properties, and which of them, if any, may alter the chemotherapeutic activity of added sulfonamides, arsenicals, etc.

Vehicles, bases, etc.:- Progress has been made as to the irritative properties of such substances, their effect on enhancing the penetrability of mercury and sulfonamides and their stability. This work, which has only recently begun, should be rapidly pushed.

Subsequent to the above presentation of work already accomplished, the meeting broke up into smaller sub-groups, appointed by the Chairman as follows:-

Sub-group on syphilis:- Chairman Dr. Eagle, with Drs. Fleming, Tatum, Mahoney, Warren, Williams, Sweet, Arnold, Guest, and Boak.

Sub-group on gonorrhoea:- Chairman Dr. Cox, with Drs. Carpenter, Herrold, Miller, Hill, Cohn, Fyar, and Shronts.

Sub-group on minor venereal diseases:- Chairman, Dr. Rake, with Drs. Greenblatt, Combes, Canizares, and Deibert.

Sub-group on vehicles:- Chairman Dr. Calvery, with Drs. Thompson, Sanders, Ackerman, Freyza, and Stokinger.

The purpose of these sub-groups was to consider desirable future points of attack, methods, and investigators. After a lapse of two hours, during which the sub-groups met, the entire Conference reconvened and the Chairmen of the respective sub-groups reported as follows:-

#### DR. EAGLE FOR THE SUB-GROUP ON SYPHILIS

A. Calomel:- Certain additional studies as to calomel require prosecution, as a hedge against the possibility that the arsenicals may prove to be less efficacious than preliminary studies indicate. These are:-

(1) The effect of particle size. Dr. W. L. Fleming, University of North Carolina School of Public Health, will undertake this in his laboratory, and will apply for OSRD contract.

Dr. Thompson will furnish Dr. Fleming with 3 ointments of particle sizes averaging 25, 5, and 1 micron, respectively. Each of these ointments will be tested in a significant number of rabbits, using the scratch method of inoculation, in varying doses in mg/kg.

Since in the experience reported by both Eagle and Mahoney, the incidence of symptomless infection in animals used in prophylactic experiments is negligibly small, it is agreed that in Fleming's and other experiments, the appearance or non-appearance of a chancre at the point of inoculation will be used as a criterion of the success of prophylaxis; this to be checked by holding one-third of the apparently protected animals for subsequent lymph node transfer at 6 months.

(2) The effect of vehicles on the efficacy of calomel. Drs. Warren and Carpenter, and Boak, University of Rochester, will undertake a study of the effectiveness of calomel in preventing syphilis in the rabbit in three vehicles:- (a) the traditional lanolin-petrolatum ointment, with which they will repeat and confirm data already available; and two ointments to be suggested by Dr. Calvery consisting of the two extremes; (b) a simple oil-in-water base; and (c) a simple water-in-oil base. \*

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\* It is not yet clear whether Warren and his associates will require supplementary funds for this study.

(3) The effect of penetrants. Dr. J. F. Mahoney and his associates at the Venereal Disease Research Laboratories of the U. S. Public Health Service at Stapleton, N.Y., will, using a single base, (probably the lanolin-pectrolatum base used in most previous studies) determine the effect of two or three representative but chemically different surface active agents. The precise ones to be used from among e.g., the alkyl sulfate or the substituted ammonium series are to be decided by correspondence between Mahoney and Calvery. An OSRD contract for Mahoney is probably unnecessary except for possible holding of personnel.

(4) The effect of added sulfonamides on the prophylactic efficacy of calomel ointment. Dr. Eagle will undertake this in his own laboratory.

B. Arsenicals: (1) It was the consensus that it would be prohibitively time-consuming and expensive to study all available compounds known to be relatively active and non-toxic (arsenicals in particular). Instead it was decided that a few compounds of widely varying in vitro treponemicidal activity would be assayed with respect to their prophylactic activity in the rabbit, in order to confirm or disprove the thesis that in vitro activity is a measure of prophylactic value. The arsenicals chosen should be stable in solution or in ointments and non-irritating on the mucous membranes of animals. Dr. Eagle will carry out this experiment in his own laboratory.

(2) Mahoney will use an arsenical the prophylactic efficacy of which will be assayed in the skin (by Eagle) for study on the genital mucosa of the rabbit, in order to determine whether these two methods of assay yield comparable results with respect to minimal concentration and time intervals of efficacy.

(3) For one or two of the most promising arsenicals should be determined the effect of vehicle, penetrant, and added sulfonamide. Unfortunately, there is an apparent dearth of cage space and personnel for the immediate study of all these factors; and some of them must in any case wait on further animal studies by Calvery and his group.

Drs. Mahoney, Fleming, Warren, and Boak, Sweet, and Tutum agree to survey their facilities and communicate with Dr. Eagle as to what could be done in the immediate future, or if not now, when release of cage space by virtue of other completed experiments would permit these studies to begin.

C. The direct effect of penetrants in the prevention of syphilis in the experimental animal:— Carpenter (see report above) and, earlier, Mahoney have shown that certain of these substances have an in vitro treponemicidal effect. Mahoney and his group have likewise studied the prophylactic activity of some of them applied to the genital mucosa of the rabbit. In their hands, some which are active in vitro are devoid of activity in vivo. Nevertheless, it seems desirable to restudy some of those with marked in vitro activity with respect to their prophylactic value when applied to a superficially inoculated area of the skin. Dr. Eagle will undertake this in his own laboratory.

D. Reasons for the concurrent study of calomel, arsenicals, and penetrants:—

Since the efficacy of calomel has already been demonstrated, it seems desirable to carry on studies of methods of improving its efficacy simultaneously with the studies on arsenicals and penetrants outlined above. If either of the latter show real rather than preliminary, promise, the calomel work can be immediately curtained or, if necessary, abandoned.

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DR. COX, FOR THE SUB-GROUP ON GONORRHEA

A. The sub-group reiterates its belief in the essential necessity of human experimentation, but makes no further recommendations in this respect, pending action by CMR-OSRD.

B. The local treatment of acute gonorrheal urethritis as an index of prophylactic activity. If a chemical compound applied locally can be shown to be curative ( see Cohn's report above), there is reason to believe that it will be of prophylactic value. Such therapeutic studies serve as a screen of chemical substances, but do not define their time relationships in prophylaxis. Arrangements have already been made to test 4 different ointments (prepared by Dr. Thompson), e.g., 5% and 20% sulfanilamide, and 5% and 20% sulfathiazole in the clinics of Cox, Cohn, and Deibert. As soon as the non-irritating properties of the arsenicals have been demonstrated in animals by Calvery and his group, arsenical ointments or jellies (to be prepared by Calvery, Thompson, Sweet, et al ) should be similarly tested. Likewise should be tested calomel ointment containing sulfonamides (if sulfonamides alone are shown to be of value).

Additional clinics should be enlisted. In addition to those of Cox, Cohn, and Deibert, mentioned above, there were suggested those of Herrold in Chicago, Deakin in St. Louis, and those under the supervision of Carpenter in Brunswick, Ga., and Jacksonville, Fla. The drawbacks of using ambulatory patients were discussed, and Dr. Cox, as chairman of the sub-group, will write to Dr. R. A. Vanderlehr, Assistant Surgeon General, U. S. Public Health Service, as to the feasibility of utilizing hospitalized patients in U. S. Marine Hospitals for such studies. In certain locations (Boston, St. Louis, Baltimore, Chicago) laboratory cooperation could be supplied to Marine Hospitals through Cox, Deakin, Hill, and Herrold.

It was agreed that for the evaluation of any single ointment, 20 cases would be adequate. Five of these should serve as controls, treated locally with the ointment base without added chemical, and 15 as the experimental subjects. All patients should receive an oral placebo, in order to minimize the chance of self-administered sulfonamide therapy. Patients should have received no previous treatment, and in all cases this should be checked by preliminary testing for urine sulfonamides. Treatment should extend for an exact period of 5 days, the drug administered locally once or twice daily, and the results checked in the usual manner by clinical examination, smears, and cultures. The records should be kept on the history forms approved by the American Neisserian Medical Society; and completed records should be sent to Dr. Cox for analysis.

C. Animal experimentation:- The encouraging report of Hill (see above) calls for immediate energetic prosecution of this work in her own and in an independent laboratory. It was agreed that Miller, University of Chicago, will make an immediate proposal for OSRD contract for this purpose; and in addition for study of the possibility of producing conjunctival infection in animals (a) on a vitamin A deficient diet; (b) with conjunctivae injured by ultraviolet light; (c) infected with myxoma virus, which produces peculiar conjunctival damage; and (d) with lacrymal glands surgically removed, to avoid the bactericidal effect of tears; and also in addition, for certain further in vitro studies (see next paragraph).

D. Further studies of gonococcal infection of the chorio-allantoic membrane of the chick:- The difficulty of separating in vitro and in vivo effect in Bang's experiments (see above) was discussed, as was also the potential value of further study of the method. Hill (also see above) has currently in progress certain experiments in amplification of Bang's work which should, within a few weeks, determine whether the method holds any advantage over simpler in vitro tests. Pending the outcome of Hill's experiments, the sub-group made no recommendations.

E. In vitro studies:- Discussion was held of the discrepant methods so far used by Miller, Carpenter, and Hill. It was agreed that these investigators would compare their several methods in in vitro tests of certain arsenical compounds to be furnished by Eagle, Sweet, and Rake. For this purpose Dr. Miller will require funds (also see Paragraph D. above) and will apply for OSRD contract.

Dr. Carpenter will confer with Dr. Warren as to this and other commitments (their existing OSRD contract; also see Paragraph A-2 under Syphilis-calmet above), to determine if additional funds are essential and if so the minimum amount.

\* \* \* \* \*

DR. CALVERY. FOR THE SUB-GROUP ON VEHICLES AND PENETRANTS AS AFFECTING ABSORPTION, TOXICITY (LOCAL AND GENERAL) AND SENSITIZATION.

"The proposal of this group is to carry on work similar to that described this morning, wherein we will study the irritating properties of chemical agents used in ointment bases, local and systemic toxicity. The penetration of chemotherapeutically active agents will be studied by chemical analyses of tissues, organs, blood, and urine until we know definitely the order of penetration of one substance with one ointment type of base, and use that as our standard of comparison for each of the types of active substances. We must follow calmet under standard conditions, keeping constant area time, amount of material applied, etc. We will study arsenicals and sulfonamides in the same way. That, then, is the general program of the group with reference to components of the bases and final preparations.

"Sander will prepare any of these materials that we wish in quantities sufficient for experimental work, supplementing Thompson's statement that he will also prepare materials, not only for laboratory experimental work but, unless the burden becomes too large, for some of the clinical work. This will be done without cost to

O.S.R.D. Sander can and will do some irritation studies. Thompson will do sulfonamide absorptions, supplementing and checking work that we are doing. Stokinger states that his laboratory can, if necessary, and if given financial support, carry out similar studies. Dr. Warren agrees to provide spectrographic analyses for both mercury and arsenic. We will have the chance, then, to check each phase of the work in at least two laboratories.

"Studies of systemic toxicity will probably be confined only to our laboratory."

\* \* \* \* \*

DR. RAKE, REPORTING FOR THE SUB-GROUP ON MINOR VENEREAL DISEASES

A. Chancroid: The sub-group agreed that all further experimentation should be carried on with cultures, not by auto-inoculation.

Additional information as to optimum methods of culture is desirable, especially as to (1) methods of preventing clumping, of affording uniform suspension, and thereby of determining minimum infective dose, (2) methods of maintaining virulence at a more stable level than is now available. With this information, a better quantitative inoculum for man can be developed than is now available. Suggested investigators for this purpose were Sanderson and Dienst, University of Georgia (OSRD contract probably necessary), Anna Delaney, University of Tennessee, Memphis, and Beard and/or Heaton, Lederle Laboratories (Chairman Moore to communicate with these two latter).

Nevertheless, and with culture methods now available, it was felt that experiments should be carried out at once (Greenblatt, Combes, and Canizares) to determine if possible the minimum infective dose which will provide from 75 - 100 per cent of takes in control inoculations.

It was agreed that further investigation of chancroidal infection in chick embryos (developed by Anderson and Godpasture) should be prosecuted; and that this should be pursued by Rake himself, Dienst (Georgia) and Hill (Johns Hopkins).

As to test inoculations in human volunteers, it was agreed that

- (a) both normal persons and those infected with chancroid should be used,
- (b) preliminary skin tests (Ito-Rienstierna) to be carried out in all volunteers,
- (c) patients with negative and positive skin tests to be used in equal numbers in each experiment,
- (d) compounds for prophylactic testing to be supplied to all investigators through Dr. Moore,
- (e) no further testing of compounds from individual pharmaceutical houses,
- (f) investigators already available:-- Greenblatt, Combes and Canizares,

(g) potential investigators:- Deibert, U.S. Public Health Service, Hot Springs, Ark., (Dr. Moore to request U.S. Public Health Service permission), Warren and Carpenter at Jacksonville, Fla. Clinic,

(h) exact details of proposed procedure to be drawn up by Dr. Rake and circulated for comment, after which all clinical work will follow exact technic as closely as possible.

(i) completed records to be forwarded to Greenblatt for collation.

B. Lymphogranuloma venereum.- No recommendations. Human experimentation is too dangerous. Cutaneous inoculation in guinea pigs will be tried by Dr. Rake, and if successful, prophylactic substances studied in those animals. A second group (Pappenheimer?) should if possible be enlisted in this study.

C. Granuloma inguinale:- Auto-inoculation of already infected persons will be tried by Greenblatt, Combes, and (with U.S. Public Health Service consent) Deibert.

The faint lead of possible infection of dogs should be followed (Greenblatt).

\* \* \*

The meeting then adjourned.

J. E. Moore, M.D., Chairman,  
Subcommittee on Venereal Diseases  
National Research Council.

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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

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NATIONAL RESEARCH COUNCIL

SUBCOMMITTEE ON VENEREAL DISEASES

of the

COMMITTEE ON MEDICINE

Minutes of a Conference on Human Experimentation in Gonorrhoea  
Held under the Auspices of the Subcommittee on Venereal Diseases.  
December 29, 1942.

On December 29, 1942, there was held at the National Research Council, Washington, under the auspices of the Subcommittee on Venereal Diseases, a conference on the subject of the chemical prophylaxis of gonorrhoea in human volunteers. Present were the following:-

From the Subcommittee on Venereal Diseases Dr. J. E. Moore, Chairman, Doctors Oscar Cos, and Russell Herrold.

The following conferees: In possible experimental studies in New York City and New York State Doctors Alfred Cohn and Theodore Rosenthal, New York City Health Department, and Doctors James H. Lade and M. Uccello, New York State Health Department.

Representing possible experimental work in the State of Georgia, Dr. Charles M. Carpenter (Mr. Royal Mann, Chairman Prison Parole Commission of Georgia, who had been invited, telegraphed his inability to be present).

Representing possible experimental work in the State of Illinois, Dr. C. Phillip Miller, University of Chicago.

From the National Research Council, Dr. O. H. P. Pepper, Chairman Committee on Medicine, Dr. T. P. Forbes, Dr. C. A. Carden, Dr. Wilbur Davison.

Statistical consultants: Dr. Lowell J. Reed, Johns Hopkins University, and Dr. Hugo Muench, International Health Division, Rockefeller Foundation.

From the U. S. Army, Lt. Col. T. B. Turner, Major Gaylord W. Anderson, Major Thomas H. Sternberg, Major Robert Dyar, Captain Robert H. Riedel.

From the U. S. Navy, Lieut. J. V. Chronos; and British Liaison Officer Commander R. W. Mussen, R.N.

From the U. S. Public Health Service Assistant Surgeon General R. A. Vonderlehr, Division of Venereal Diseases.

The Chairman opened the meeting with an initial statement regarding the incidence of gonorrhoea in the U. S. Army and Navy, the number of probable cases if the current incidence is not reduced, and the number of lost man days from this cause. It was pointed out that new and improved methods of prophylaxis of gonorrhoea were essential and that these methods, because of the lack of a suitable experimental animal

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and the inability to transfer in vitro laboratory studies directly to man, could only be determined by means of the crucial human experiment. It was pointed out that the Subcommittee on Venereal Diseases has been interested in the possible human experimentation in general since its inception in June 1940, and the previous unsuccessful efforts to accomplish this in volunteer personnel of the U. S. Army and Navy had been <sup>made</sup> through the initiative of Dr. Charles M. Carpenter, University of Rochester, tentative plans for carrying out such experimentation in volunteer prison inmates in the State of Georgia had been brought to the attention of the Subcommittee on Venereal Diseases. Almost simultaneously Dr. Alfred Cohn of New York City had developed tentative plans for such studies at the Ryker's Island House of Correction.

These tentative proposals of Doctors Carpenter and Cohn had made it seem essential to obtain expressions of opinion regarding the desirability of such human experimentation from the Surgeons General of the U. S. Army, Navy, and Public Health Service. The matter having been brought to the attention of these officers, letters were written by the respective Surgeons General to Dr. Lewis Weed, Chairman Division of Medical Sciences, National Research Council, as follows:-

(Three letters follow as pages 3, 4, and 5)

C In reply refer to SP/CA

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WAR DEPARTMENT  
OFFICE OF THE SURGEON GENERAL  
WASHINGTON

December 4, 1942

Dr. Lewis H. Weed  
National Research Council  
Washington, D.C.

Dear Dr. Weed:

It is understood a proposal has been made that the National Research Council undertake an investigation in search of an effective prophylaxis and improved treatment for gonorrhoeal infections, using selected human volunteers.

It is unnecessary to reaffirm the interest of this office in any scientific research the object of which is to reduce the incidence of this social disease, particularly in an armed force. Any progress in this field will have a direct bearing on the conservation of manpower engaged in war work of any character and it is hoped it will be possible for the Council to undertake such an investigation.

Very sincerely yours,

S/ John A. Rogers  
Colonel, Medical Corps  
Executive Officer

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Department of the Navy  
Bureau of Medicine and Surgery  
Washington, D.C.

Y-mlp

December 5, 1942

Do not address the signer of  
this letter, but address  
reply to Bureau of Medicine  
and Surgery, Navy Department,  
Washington, D.C.

and refer to No.  
P3-2/P3-(121)

My dear Doctor Weed:

The incidence of gonorrhoea in the armed forces and the  
lost manpower resulting therefrom constitutes a problem of major  
military importance. New and improved methods for the prevention  
of gonorrhoea are urgently desirable. Unfortunately, adequate exper-  
imental studies cannot be carried out in animals, since no known  
animal species is susceptible to local infection with the gonococcus.  
Laboratory studies other than in experimental animals do not provide  
definitive information capable of translation to man. The crucial  
experiment in the development of new prophylactic agents against  
gonorrhoea lies in the experimental inoculation of human volunteers.

It is hoped that such experimental studies in human  
beings may be undertaken under the auspices of the National Re-  
search Council.

Sincerely yours,

W. S. ROSS TO McINTIRE  
Surgeon Admiral (MC)  
Surgeon General, U. S. Navy

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

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UNITED STATES PUBLIC HEALTH SERVICE

Washington, D.C.  
(Bethesda Station)

November 19, 1942.

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

Dear Doctor Weed:

I have been informed that Doctor Charles M. Carpenter of the Strong Memorial Hospital of Rochester, New York, is interested in studies of the epidemiology and prophylaxis of gonorrhea and that the plan involves the utilization of human subjects for experimental inoculation by laboratory methods. No laboratory animals are available for this work inasmuch as such animals cannot be successfully inoculated with the gonococcus.

Because of the great prevalence of gonorrhea and its importance in the production of noneffective man-days both in the armed forces and civilian population, I believe that the human inoculation experiments proposed by Doctor Carpenter are justifiable if the human subjects are selected on a voluntary basis. The work should contribute some worthwhile new findings in the epidemiology and prevention of gonorrhea.

Sincerely yours,

S/ Thomas Parran

Surgeon General

Cc: Dr. Moore

The entire question of human experimentation in gonorrhoea was considered at a meeting of the Subcommittee on Venereal Diseases on December 1, 1942, and a recommendation approved as follows:-

"THAT HUMAN EXPERIMENTATION IN THE PROBLEMS 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 HPC, OMP, 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 SHOULD BE SELECTED BY THE CHAIRMAN SUBCOMMITTEE ON VENEREAL DISEASES. THE PROPOSALS OF DR. CHARLES M. CARPENTER, ROCHESTER, NEW YORK, AND DR. ALFRED J. 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."

This recommendation was further considered and approved by the Committee on Medicine, National Research Council, at its meeting on December 10, 1942.

The approval of this recommendation was transmitted to Dr. A. N. Richards, Chairman Committee on Medical Research, on December 11, and resulted in the following reply from Dr. Richards:-

(Letter from Dr. Richards p. 7)

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Office for Emergency Management  
COMMITTEE ON MEDICAL RESEARCH  
of the  
Office of Scientific Research and Development  
Washington, D.C.

December 12, 1942.

Dr. J. E. Moore  
804 Medical Arts Building  
Baltimore, Maryland.

Dear Doctor Moore:

I understand from your letter of December 11 that the proposals of Dr. Charles M. Carpenter and Dr. Alfred M. Cohn for experimentation on human subjects in the prophylaxis of gonorrhoea, while approved in principle by the Subcommittee on Venereal Disease and the Committee on Medicine, await further discussion by the Conference which you propose before being submitted to the Committee on Medical Research.

I believe it would be appropriate for you to call a meeting of the proposed conference group immediately so that the final definition of the proposals may be before the Committee on Medical Research as soon as possible.

If the prosecution of the investigations is dependent upon contracts with OSRD, it would not seem wise to approach the State authorities until contracts are assured.

The wording of the recommendation is such as to lead me to remark that OSRD will not execute a contract with an individual physician, but only with the institution ( University or Hospital) of which he is a member. It would be well to see to it that the responsible institutional authority who endorses the application for contract is made fully aware of the content of the proposal.

When the proposals are submitted to the Committee on Medical Research, I suggest that copies of the letters referred to in the first paragraph of your letter be attached for inclusion in our files.

Very truly yours,

S/ A. N. Richards, Chairman  
Committee on Medical Research

The Chairman then outlined the agenda of this Conference meeting to include three topics:-

- 1) The preparation of proposals for OSRD contract by potential contract holders for human experimentation in prisons, namely, Doctors Carpenter, Miller, and Cohn.
- 2) The method of approach to the State authorities of Georgia, New York, and Illinois, and the City authorities of New York, and
- 3) The drawing up of a planned outline of attack.

Dr. Carpenter reported on a conference which he had held with the Prison Parole Commission and with the State Health Department of Georgia in Atlanta on November 16, 1942. Present at this conference were Mr. Royal K. Mann, Chairman of the Prison Parole Commission, Dr. Thomas W. Abercrombie, Commissioner of Health, Dr. Dan Bowdoin, Director of the Division of Preventable Diseases, State Department of Health, Dr. John Walton, Venereal Disease Control of Prisons, State Department of Health, Dr. Percy Pelouze, U. S. Public Health Service, and Dr. Carpenter.

Chairman Mann expressed his interest in cooperating in such an investigation and requested that an outline of the project be prepared and submitted to him for presentation to the other members of the Prison Parole Commission and to the Attorney General.

Dr. Carpenter prepared such an outline which he submitted to Mr. Mann on November 22nd. This outline and the covering letter to Mr. Mann are reproduced herewith, including as an appendage thereto the resolution prepared by the American Neisserian Medical Society on October 22nd, 1942.

University of Rochester  
School of Medicine and Dentistry  
Rochester, New York

November 22, 1942.

Mr. Royal K. Mann, Chairman,  
Prison Parole Commission,  
Atlanta, Ga.

Dear Mr. Mann:

At our meeting on November 16 with Doctors Abercrombie, Bowdoin, Walton, and Pelouze, you requested that an outline of the proposed project on the evaluation of venereal disease prophylactics be submitted to you for presentation to your Commission and to the Attorney General. I hope that the enclosed statement adequately covers the essential points.

The control of venereal disease is one of the major problems in our armed forces. The enormous loss of time in manpower and the vast cost of these diseases need not be emphasized to you or your Commission. Knowledge of the treat-

Mr. Royal K. Mann

November 22, 1942

ment of gonorrhoea has advanced markedly in recent years, but the urgent problem today is the prevention of venereal diseases, and particularly gonorrhoea. Exhaustive studies by medical scientists have failed to discover an experimental animal on which such tests could be made. It is essential, therefore, to evaluate prophylactic measures on man, and because of the remoteness of any danger in such a study, it is urged that this important work be undertaken. The reasons for selecting a penal institution for such a study are set forth in the outline of the proposed project. By cooperating in this work, both the State and the institution can render an unusually valuable service to the war effort.

Since our recent meeting, I attended a conference on venereal disease prophylaxis in Washington on November 18, in which representatives of the National Research Council, and of the Medical Corps of the Army, Navy, and Public Health Service participated. The group was united in proclaiming venereal disease prophylaxis as one of the important medical problems of the armed forces, and in agreeing that an investigation of venereal disease prophylactics be carried out as promptly as possible in a penal institution where the subjects were under control and could be carefully supervised. Letters from the Surgeons General of the Army, Navy, and Public Health Service, reiterating this recommendation will be forwarded to you. A copy of a resolution approved by the American Neisserian Medical Society is enclosed. For your information, this society is comprised of about 400 of the leading physicians in the United States who are concerned with the treatment and control of gonorrhoea.

Our desire is to carry out this study in the State of Georgia because of the excellent cooperation offered in other medical projects. During the past year I have been carrying on a study of the prevalence and control of gonococcal infection in Glynn County in cooperation with the Glynn County Board of Health, the Georgia State Department of Health, and the United States Public Health Service. The Office of Scientific Research and Development and the U.S. Public Health Service have requested that a suitable institution be located for this study before funds are made available to carry out the work.

Because of the urgency of getting the work under way promptly, I hope that this information can be brought to the attention of your Commission in the near future, and that it will be received favorably by them and by the Attorney General. I am very appreciative of your cooperation and trust that permission to undertake the work will be granted.

Sincerely yours,

S/ Charles M. Carpenter, M.D.  
Associate Professor of Bacteriology,  
University of Rochester School of Medicine  
& Dentistry,  
Special Consultant, U.S. Public Health Service  
Responsible Investigator for Office of  
Scientific Research and Development.

Dr. Carpen's statement on  
THE EVALUATION OF PROPHYLACTIC AGENTS AND PROCEDURES  
IN THE PREVENTION OF GONORRHEA

Proposed Project to be Carried out in Penal Institution

The control of venereal disease constitutes one of the major current medical problems, not only in the armed forces but in the civil population. During the World War venereal disease was responsible for the loss of seven million man days in the American forces. Each year in the United States a million and a half new cases of venereal disease occur. Gonorrhoea comprises the greatest majority of these infections. With the development within recent years of sulfonamide compounds, an effective treatment of gonorrhoea has become available; the chief problem, however, is prevention of the disease. Because this is of paramount importance in the armed forces, the present studies on prophylaxis would be confined to the prevention of the disease in men.

General Information

Gonorrhoea cannot be produced experimentally in animals; the testing of prophylactic measures must, therefore, be carried out on man. To provide accurate, dependable information, it is essential that subjects be under complete control during the period of observation, and that there be no sexual contact with women. For that reason it is desirable that the work be conducted in a penal institution. The use of human volunteers in state institutions has been successfully utilized in the past in a number of instances, particularly in studies on pellagra and on St. Louis encephalitis.

The plan is to limit the studies entirely to volunteers. In some studies the prison commission has enlisted the cooperation of the inmates by offering some inducement such as a shortened sentence. The dangers from the proposed investigation on the prophylaxis of gonorrhoea would be remote and the procedure would be explained to volunteers before they were included in the study. Because of the medico-legal responsibility, waivers should be obtained from participants, and adequate insurance carried by the investigators. A trained physician would supervise the work and would be available at all times.

Purpose of Investigation

The purpose of the investigation would be to study the effectiveness of two types of prophylaxis against gonorrhoea: (1) the protective action of sulfonamide compounds taken by mouth before exposure to the disease, and (2) the prophylactic action of chemical agents applied locally to the genital tract after exposure to the disease.

Procedure

Volunteers would be examined to determine if they were free from gonorrhoea and then would be placed in one of the following groups:-

Dr. Carpenter's statement cont'd

(1) One group would be given sulfonamide compounds by mouth, following which they would be exposed to the infection. Frequent observations would be made to detect signs of the disease. This method of prophylaxis is in use in certain army camps, but it has not been tested under controlled conditions. The subjects would also be observed for possible development of sensitivity to the drug and also to determine if they became carriers of the infection.

(2) A second group would first be exposed to the infection, after which chemical prophylactic agents would be applied locally to the external genital organs. This routine chemical procedure as carried out in the armed forces has never been adequately tested. Furthermore, since the first World War new chemical agents have been developed which promise far better results and which require testing.

(3) A third group of volunteers would be retained as controls for the first two groups. This would provide necessary information on the susceptibility of man to the infection. As previously stated, an effective method of treatment is available for those men who develop signs of the disease.

#### Required Facilities

To carry on the study, certain facilities would be essential: (1) a clinic or examination room; (2) general hospital facilities for any patients who might need special care; (3) a laboratory equipped to carry out bacteriological examinations; (4) quarters for personnel, consisting of one full-time physician, one part-time physician, one bacteriologist, and one technician. At least 100 men free from gonorrhea would be needed for the study. This might require that several hundred volunteers be solicited and examined before a sufficient number suitable for the study could be selected. The duration of the study would be about one year.

(Enclosure in letter  
to Mr. Royal K. Mann-2)

AMERICAN NEISSERIAN MEDICAL SOCIETY

November 2, 1942

Office of the Secretary  
475 Commonwealth Ave.  
Boston, Mass.

The American Neisserian Medical Society, at its eighth annual meeting held in Hot Springs, Arkansas, on October 22, 1942, voted that it was the opinion of the Society that immediate steps should be taken to carry out scientific studies in the field of prophylaxis of gonococcal infection: that, since no experimental animal is susceptible to such infection, the studies must depend upon human volunteers, and because of the enormous loss of man power in the armed forces caused by gonococcal infection, it is urgent that such studies be undertaken without delay.

S/ Oscar F. Cox, Secretary  
American Neisserian Medical Society.

On November 23rd Dr. Carpenter submitted to Dr. Moore, Chairman Subcommittee on Venereal Diseases, a somewhat more detailed description of his contemplated plan of procedure, including a statement of explanation to tentative volunteers. This proposed project of Dr. Carpenter's for OORD contract was, as noted above, approved in principle at a meeting of the Subcommittee on Venereal Diseases on December 1, subject to such modifications as might be made in it by this Conference.

On November 27, 1942, Dr. Cohn submitted to the Subcommittee on Venereal Diseases a tentative proposal for similar experimentation in the prisons of New York City and this proposal was also approved in principle by the Committee on Medical Research. Dr. Cohn reports that in the meanwhile he has investigated the situation further, both with the City and State health authorities; and that the situation now appears less favorable than it did when his informal application was submitted.

Dr. Rosenthal of the New York City Health Department reports that on Dr. Cohn's behalf Commissioner Stubbins and himself consulted the Corporation Counsel of New York City, from whom a verbal and informal opinion has been obtained that legal objection to such experimentation in New York City or State may be made. The State Penal Code includes a definition of "maiming" which seems, in the opinion of the Corporation Counsel to preclude the carrying out of the study in New York. This section of the Penal law of New York State follows:-

ROCKWELL'S PENAL LAW - Book 39

SECTION 1400 MAIMING DEFINED: punishment

A person who wilfully, with intent to commit felony, or to injure, disfigure, or disable, inflicts upon the person of another an injury which:

1. Seriously disfigures his person by any mutilation thereof;
- or,
2. Destroys or disables any member or organ of his body; or,
  3. Seriously diminishes his physical vigor by the injury of any member or organ,

Is guilty of maiming, and is punishable by imprisonment for a term not exceeding fifteen years.

The infliction of the injury is presumptive evidence of the intent.

1. PRIOR LAW- COMMON LAW RULE

"Meyhem et common law is defined by Blackstone as the violently depriving another of the use of such of his members as may render him less able in fighting either to defend himself or to annoy his adversary. (4 Black.204.) It was recognized as a felony at a very early period of the common law, and the offender was punished by the loss of the same member of which he had deprived the party maimed; membrum pro membro. It was treated as an offense against the State, for the reason assigned by Lord Coke (1 Inst. 127): "for the members of every subject are under the safeguard and protection of the law, to the end a man

"may serve his king and country when occasion shall be offered.' The special injuries which constituted mayhem are stated by Hawkins as follows: 'And therefore the cutting off or disabling or weakening a man's hand or finger, a striking out his eye or foretooth, or castrating him, are said to be maims; but the cutting off his ear or nose are not esteemed maims, because they do not weaken, but only disfigure him.' (1 Hawkins' Pleas of the Crown, 107)"

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SECTION 1401 WHAT INJURY MAY CONSTITUTE MAIMING

To constitute maiming, it is immaterial by what means or instrument, or in what manner, the injury was inflicted.

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SECTION 1402. MAIMING ONE'S SELF TO ESCAPE PERFORMANCE OF A DUTY

A person who, with design to disable himself from performing a legal duty, existing or anticipated, inflicts upon himself an injury, whereby he is so disabled, is guilty of a felony.

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SECTION 1403 MAIMING ONE'S SELF TO OBTAIN ALMS

A person who inflicts upon himself an injury, such as if inflicted upon another would constitute maiming, with intent to avail himself of such injury, in order to excite sympathy, or to obtain alms, or any charitable relief, is guilty of a felony.

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SECTION 1404 SUBSEQUENT RECOVERY OF INJURED PERSON, WHEN A DEFENSE

Where it appears, upon a trial for maiming another person, that the person injured has, before the time of trial, so far recovered from the wound, that he is no longer by it disfigured in personal appearance, or disabled in any member or organ of his body, or affected in physical vigor, no conviction for maiming can be had; but the defendant may be convicted of assault in any degree.

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However, Dr. Cohn and Dr. Rosenthal emphasize the fact that this legal opinion is tentative, not final, and that it may perhaps be altered by further consideration, particularly if the proposal is supported by the type of national backing which is, as indicated above, now available. Dr. Cohn suggests that if his proposal for OSRD contract is approved by CMR -OSRD, a meeting be held in New York City, to be attended by a representative of NRC or CMR, preferably Dr. J. E. Moore; of the following persons: Commissioner of the New York City Health Department Dr. Stebbins, Commissioner Department of Correction, Dr. Amoroso, a representative of the office of the Attorney General of the State of New York, a representative of the Department of Health of the State of New York, a representative of the City Corporation Council, a representative of the State Department of Correction, and in addition, Doctors George Baehr, Walter Clarke, Theodore Rosenthal, and Alfred Cohn.

It was pointed out that Dr. Cohn's original contact had been with the authorities of the City of New York, but that if New York State could be brought into

the picture, other prison populations might be made available and that conceivably Dr. Cohn could work not only at Ryker's Island, New York City, but also in Sing Sing Prison, and that Dr. Carpenter might be able to carry out similar experiments in Attica Prison, about 40 miles from Rochester.

Dr. Lade, speaking for the New York State Health Department, reports that he has discussed the question of human experimentation in gonorrhea with the State Commissioner of Correction, and has obtained from this official a verbal comment that he would favor such a study in New York prisons. The Commissioner of Correction offered a written commitment but Dr. Lade believes that he did so without knowledge of the Penal Code quoted above, and that the attitude of New York State officials would depend on the outcome of an approach made to the New York State and City authorities by the National Research Council.

Dr. Miller reports that he has made tentative arrangements for the carrying out of human experimentation in the Stateville branch of the Illinois State Penitentiary near Joliet and submits a letter from Mr. T. P. Sullivan, Director, Department of Public Safety, State of Illinois, which is quoted herewith:

STATE OF ILLINOIS  
DEPARTMENT OF PUBLIC SAFETY

December 21, 1942

Dr. C. Phillip Miller  
Department of Medicine  
University of Chicago  
Chicago, Ill.

Dear Dr. Miller:

With further reference to the study of the treatment and prevention of gonorrhea, which you desire to make for the Subcommittee on Venereal Diseases of the National Research Council, at the hospital located in the Stateville Branch of the Illinois State Penitentiary near Joliet, Illinois, I want to again assure you of the full and complete cooperation of the Department of Public Safety of the State of Illinois.

I have conferred with the Warden, Joseph E. Ragen, and the resident physician, Dr. Chuselik, and they are confident that you will experience little difficulty in obtaining volunteers from the inmate body of the institution to make these scientific tests. The warden has also assured me that the physical set-up of the prison hospital will permit complete isolation during the period of infection and treatment.

I have also conferred with Governor Dwight H. Green regarding this project, and he has directed me to advise you and your associates that the State of Illinois, through its various departments, will render every assistance possible in this research so important to the health of our armed forces.

I want you to feel free to direct our efforts in order that we may give you the best cooperation possible.

Yours very truly,

S/ T. P. Sullivan, Director.

Dr. Vonderlehr was asked for the names of other states in which such human experimentation might conceivably be carried out in State prison institutions, and replied that in his opinion almost any state in the South might be approached. Pressed for the names of specific states, he suggested Alabama, North Carolina, Mississippi, and Tennessee. He emphasized, however, that in his opinion it was desirable to make haste slowly; that preliminary studies on a limited scale were desirable before attempting more elaborate investigations; and that every effort should be made to avoid publicity.

As a result of this discussion and in consideration of the third paragraph of Dr. Richards' letter, noted above, it seemed clear that Doctors Cohn, Carpenter, and Miller should prepare applications for OSMD contract; that these applications should include an exact statement of the proposed method of experimentation, of the risks involved, and of the explanation to be made to tentative volunteers. It was apparent that in the cases of Doctors Carpenter and Cohn the applications could provide only tentative estimates of expense, since exact details of the expense of personnel, equipment, etc., could not be determined until the actual permission to proceed had been obtained from the responsible State authorities. Dr. Richards' letter, moreover, made it clear that the State authorities should not be approached until after the OSMD contracts had been approved. It was therefore agreed that Doctors Carpenter, Cohn, and Miller would, at the earliest possible moment also submit to the Chairman, Subcommittee on Venereal Diseases, such proposals for contract; that these, if approved by the Subcommittee on Venereal Diseases and the Committee on Medicine, could be forwarded to CMR, and if approved by CMR, authorization would be given to a representative of CMR or to the Chairman Subcommittee on Venereal Diseases to make the formal approach to the State authorities in question.

As to a statement of risks to tentative volunteers, Dr. Carpenter had drawn up such a statement in the tentative proposal which he had submitted to the Subcommittee on Venereal Diseases on November 23rd. This statement had been in the meanwhile considered by the Subcommittee on Venereal Diseases, who believed it to be desirable of amendment in certain points. It had also been sent to Dr. Miller who, in turn, had submitted it to counsel for the University of Chicago, who likewise had suggested certain amendments. These amendments were discussed by the Conference and the Chairman, Dr. Moore, was authorized to draw up a revised statement of explanation to volunteers for inclusion in the proposed plan of attack, and for submission to the legal advisor of CMR. Such a statement forms the last portion of the proposed outline of attack which follows below.

Dr. Reed next reported that an NRC Committee of Statistics had been appointed with himself as Chairman, and that this committee would be advisory not only to the Division of Medical Sciences, but also to certain other divisions of NRC. A subcommittee of this Committee on Statistics will function for medical research with Dr. Reed as Chairman. This Committee will be advisory to various NRC committees and subcommittees, not only in the formative stages of their problems, but also as the problems develop. Dr. Reed has designated as Statistical Advisor to the Subcommittee on Venereal Diseases, Dr. Hugo Lunnch, International Health Division, Rockefeller Foundation, 49 West 49th St. New York.

The conference then proceeded to a detailed discussion of an outline of experimentation, which is appended herewith as Exhibit "B".

EXHIBIT "3"

PROPOSED PLAN OF PROCEDURE IN THE STUDY  
OF CHEMICAL PROPHYLAXIS IN HUMAN  
VOLUNTEERS AMONG PRISON INMATES.

There were presented to a Conference held on December 19, 1942, in Washington under the auspices of the Subcommittee on Venereal Diseases, National Research Council, tentative proposals for the study of chemical and chemotherapeutic prophylaxis of gonorrhea in human volunteers drawn from prison inmates in the States of Georgia, Illinois, and New York, to be carried out respectively by Doctors Charles M. Carpenter, University of Rochester, C. Phillip Miller, University of Chicago, and Alfred Cohn, New York City Health Department. It was agreed by the Conference that if such human experimentation was to be carried out by different investigators working in different locations, it would be absolutely essential that the procedures to be followed were, so far as possible, identical.

The methods of procedure were considered under several different headings, as follows:-

I. Selection of subjects.

1. Only volunteers are acceptable; and these will be limited to men who have been in the institution in question for at least 3 weeks ( in order to eliminate the possibility that a volunteer may be in the incubation period of gonorrhea.) and who expect to remain in the institution for a minimum period of 6 months (in order to provide for an adequate period for study and for treatment if necessary).
2. Each volunteer will be subjected to a complete medical history and physical examination. Excluded from the study will be:-
  - a) All persons with a history of rheumatic fever or with valvular heart disease ( this because of the potential small risk in such persons of the development of gonococcal endocarditis.
  - b) All persons with a history of previous gonococcal arthritis (this because of the reported tendency of such persons to further attacks of arthritis).
  - c) All persons with abnormal genitalia (hypospadias, epispadias), (this because of the known difficulty of chemotherapeutic cure of gonorrhea in such persons).
  - d) All persons with a history of previous serious sulfonamide reactions (this because of the necessity of administration of sulfonamides, either as prophylaxis or for treatment in controlled cases or in those in whom prophylactic treatment fails to protect
  - e) All persons with obvious acute or chronic illness from any cause.
  - f) All persons who at the time of examination have gonorrhea or who have a history of having had gonorrhea or treatment for it within the past year.
3. Acceptable for the study will be persons not included in any of the categories enumerated above, who fulfill the following qualifications:-

Exhibit "B" 2

- a) A negative history of gonorrhoea or of treatment for it, within the year preceding the time of the experiment.
- b) No purulent urethral discharge, the patient to be examined in the morning before voiding.
- c) A clear urine with few or no shreds (a one-glass test to be used).
- d) Microscopic examination of the prostatic secretion will be performed and the presence or absence of clumped white blood cells recorded; but patients whose prostatic secretion contains pus will not be excluded from the study if urine cultures are negative.
- e) At least three negative cultures of urine sediment obtained by voiding after massage of the urethra and prostate, these cultures to be obtained at weekly intervals.
- f) A preliminary urine sulfonamide determination will be made, and volunteers with fulfonamide in the urine will not be employed.

4. It was recognized that in prison populations, certainly among Negroes in the South, it would be difficult if not impossible to obtain a sufficient number of volunteers who had never had gonorrhoea. It was therefore agreed that volunteer subjects would be acceptable with the qualifications described above, regardless of a history of gonorrhoea contracted more than one year before the date of the experiment. It was recognized, however, that because of varying degrees of immunity, possibly possessed by men who had had one or multiple attacks of gonorrhoea in the past, controlled and experimental groups should include in equal numbers those who (a) have never had gonorrhoea, (b) have had one to three previous attacks, and (c) have had more than three previous attacks.

II. Isolation of volunteers. It was agreed that individual isolation of volunteers is desirable, either in cell blocks or in prison hospitals, in order to prevent so far as possible any homosexual practices. In this case it was felt that volunteers known to the prison physician or prison guards to be actively homosexual should be excluded from the experiment; but that, given proper conditions of isolation, rectal cultures to determine freedom from rectal gonorrhoea, were not essential in acceptable volunteers. It was also agreed that whatever form of isolation was employed, this should not take the form of solitary confinement.

III. Method of inoculation.

1. It was agreed that a standard culture should be employed. This culture will be provided by Dr. C. Phillip Miller. It is a culture which has been carried on artificial media for 4 - 5 months, and its minimum lethal dose for the production of gonococcal septicemia in mice by means of its intraperitoneal inoculation with mucin is known to be in the general range of 100 : 1000 viable organisms.

It was agreed that the culture to be employed should be non-sulfonamide resistant and should have a low thermal death point, these factors being of obvious importance in the treatment of infected controls or of volunteers not protected by prophylaxis. These factors are not known for the culture employed by Dr.

Miller but will be determined with these cultures by Dr. Carpenter, the cultures being furnished to him by Dr. Miller.

When these factors have been determined, Dr. Miller's cultures will be used for inoculation by all of the investigators. The original cultures will be furnished to each investigator by Dr. Miller. Each investigator will utilize for the propagation of this culture the bacteriologic medium and technique with which he is most familiar. This latter proviso is inserted because of fundamental lack of knowledge as to whether cultured gonococci are infectious for man or, if so, which is the best medium for their propagation; and ultimate standardization of medium is not thereby precluded.

2. A measured inoculum will be used, to be prepared in the following manner:- charcoal absorbed broth should be utilized to wash a solid medium culture of approximately 12 - 24 hours' growth. The concentration of gonococci in the washing will be adjusted in dilution by comparison in density with a provided standard. This standard will be prepared and distributed to the other investigators by Dr. Miller.

The original suspension will then be diluted to  $10^{-7}$  (a dilution containing approximately 100 - 1000 organisms per c.c.). The number of viable organisms per ml in the inoculum employed will be determined by plate cultures and recorded.

3. The method of inoculation - 0.1 c.c., measured by tuberculin syringe, of the original inoculum, diluted as described above to  $10^{-7}$ , will be dropped into the meatus, the bladder first having been emptied, and will be retained there by gentle pressure for 5 minutes.

If a  $10^{-7}$  dilution proves to be noninfectious in each of 3 volunteers, the next lower dilutions will be employed.

IV. Inoculated volunteers, whether controls or experimental subjects, will be observed clinically every day for 3 weeks. If no symptoms of acute gonorrhoeal urethritis develop, cultures of urine sediment will be made at weekly intervals for this period. In the absence of symptoms and with negative urine cultures a volunteer will be regarded as non-infected. If symptoms develop, the diagnosis of gonorrhoea will be verified by gram stain of the urethral discharge and by culture.

V. Treatment of infected volunteers. When infection is produced, either in control or experimental subjects, the treatment to be given will consist of sulfathiazole by the routine prescribed for the treatment of gonorrhoea in the U. S. Army.

VI. The initial effort of this experiment will be to determine whether this infection can be produced in human volunteers by means of the intra-urethral inoculation of cultures of gonococci in the manner described above and, if so, to determine as accurately as possible the minimal infective dose. The latter seems essential in order on the one hand to make the prophylactic experiments correspond as closely as possible to the probable minimal infective dose of gonococci which produce the disease acquired in the natural manner; and on the other hand to avoid the possible risks of complications or of serious infections produced by an overwhelming dose. It is estimated that not more than 30 volunteer subjects will be necessary to determine these points.

VII. Chemotherapeutic prophylaxis. If infection can be produced in controls, the first prophylactic experiments will be carried out with oral sulfathiazole since this drug is being used in this manner for the prevention of gonorrhea both in the U.S. Army and Navy, but without as yet any accurate definition of time-dose relationship. Subsequently sulfadiazene and probably sulfamethyldiazene will be studied in the same manner. It is desired to determine the time-dose relationship of oral sulfonamide prophylaxis. The first experiment will therefore include the following groups:-

<u>Sulfathiazole administered</u>		<u>Experimental subjects</u>	<u>Controls</u>
<u>Time</u>	<u>Dose</u>		
2 hrs. before inoculation	2.0 gm.	10	20 - 60
6 " after	1.0 "	10	
	3.0 "	10	
12 " "	1.0 "	10	
	3.0 "	10	
24 " "	1.0 "	10	
	3.0 "	10	
48 " "	1.0 "	10	
	3.0 "	10	

The number of controls is variably set at from 20 - 60 depending upon the number of experimental subjects plus controls who can be inoculated at one time. If the entire group can be inoculated at once, 20 controls are adequate. If, on the other hand, groups must be inoculated separately for each time interval and dosage level, each group of 10 experimental subjects should be paralleled by 6 controls.

The dosage levels of 1.0 and 3.0 grams are selected advisedly on the basis of current information from Army and Navy. A total dose of 4.0 grams divided in from 2 - 4 doses has been currently utilized in both services with apparent success. It is reported, however, that of 102 men recently studied who had been given 2.0 grams before sexual exposure and 2.0 grams 2-4 hours afterwards, 38 per cent had microscopic hematuria.

During the period of sulfonamide administration, whether for experimental prophylactic purposes or for subsequent treatment, a minimum fluid intake of 2,000 to 2500 c.c. per day is required.

After the efficacy of sulfathiazole has been determined, sulfadiazene will be studied in the same manner.

Sulfamethyldiazene has been suggested as a possible desirable prophylactic agent in gonorrhea. This preparation, prepared by Charpe and Dohmo, is easily available commercially, is readily soluble, is more completely absorbed from the intestine than other sulfonamides, and is more slowly excreted. A single dose of 2.0 grams is said to maintain a blood level of 1-2 mg. per cent for 48 hours. The efficacy of the drug in acute gonorrheal urethritis in man is not known, but will be studied in the immed-

iate future by the American Neisserian Medical Society - U.S. Public Health Service cooperative clinical group. If it proves to be effective in established gonococcal infection in man, it is recommended that its prophylactic efficacy in volunteers be investigated in the same manner as described above.

It is estimated that for testing the chemotherapeutic prophylactic efficacy of orally administered sulfonamides, approximately 150 volunteers will be required for each drug so studied.

VIII. Chemical prophylaxis. A study of the prophylactic effect of various substances introduced locally into the urethra will be postponed temporarily pending the outcome of other experimental studies now in progress as to the optimum gonococcocidal substance, and the optimum vehicle for its local use. It is not yet certain whether the best available substance will prove to be an arsenical, a sulfonamide, a mercurial salt, or a silver salt. Nor is information as yet available as to the effect of the addition of penetrants, wetting agents, etc. to the ointment or jelly base. Information on these points should be available by the time of completion of the chemotherapeutic prophylactic studies outlined above, and should then be carried out in future volunteer subjects. An exact outline of these proposed experiments cannot as yet be drawn.

However, it is desirable to know whether certain of the newer chemical substances proposed for local prophylaxis are irritating when injected into the normal human urethra. Studies are now in progress of the irritating effect of such substances in experimental animals, utilizing the conjunctival sac and the vagina for this purpose. Substances obviously irritating in animals will not be employed in human beings. Those which prove to be non-irritating in animals must, however, be studied for irritating properties in human beings before their use in prophylaxis is feasible. It is hoped that such studies may be carried out in persons volunteering for the inoculation experiment with gonorrhoea but who, for one or another reason given in Section I above, prove unsuitable for this purpose.

STATEMENT OF EXPLANATION OF THE EXPERIMENT AND ITS  
RISKS TO TENTATIVE VOLUNTEERS

The following is a suggested explanation to be given to volunteers solicited for the study. This should be reviewed and if necessary amended by counsel for CMA and by legal authority in the bases in which experimentation is proposed.

"The study which we plan to carry on here, and for which we have asked your cooperation, is concerned with gonorrhoea. You may also know this disease as the 'clap', 'strain', or the 'running rashes'. Some of you have had the infection at some time in the past, or perhaps several times, and you know that it did not make you seriously sick. Recently a simple, dependable treatment has been discovered which consists of a drug taken in the form of pills.

"What we propose to try now is to develop certain methods of preventing the disease in men who are exposed to it. Gonorrhoea causes a great loss of time in the Army and Navy, and one of the important medical problems today is to discover how to prevent it in the armed forces. We believe that we have effective methods of doing this, but we cannot know for certain until they have been tested on men. It is not possible to use animals for this purpose because they are not susceptible to gonorrhoea. Therefore, we are calling on you for your cooperation. This is one way in which you can specifically help in the war effort. The benefits will not be limited to the armed forces but will be applied to the civil population as well, and it is very likely that you and your families might later profit from them.

"In the first place, I want to assure you that so far as we are able to discover, there is no reason to expect any injury from this treatment, but one cannot predict with positiveness that the result in all cases will be the same. Certain of the men may develop signs of gonorrhoea, but in almost every instance they will disappear within a few days after treatment. Most of you, however, will have no disease whatever.

"The general plan of the study is as follows:- First, you will be examined to be certain that you do not now have gonorrhoea. Those of you who are now or have recently been infected will not be accepted for the study. Then we will test methods of prevention (prophylaxis) for use in the Army and Navy, in order to determine if they will prevent the disease after exposure to the infection.

"One group of men will be given the drug sulfathiazole in the form of pills as a preventive. This will be given at different times before and after exposure to the infection, which will be carried out by applying the germ to the end of the penis. Another group will first be exposed to the infection in the same manner and shortly after will be given a prophylactic treatment. This consists of applying an ointment to the inside and outside of the penis. A third group will be exposed to the infection and later treated with sulfathiazole, if signs of the disease should develop.

"All men exposed to the infection will be examined daily for at least 3 weeks. You will be under the supervision of a physician specially trained to treat gonorrhoea and he will be available at all times throughout the study.

"Most patients with gonorrhoea can be cured within 5 to 10 days with modern treatment without experiencing discomfort or complications. A few patients with gonorrhoea do not respond to modern treatment methods (probably less than 1 in 10). These patients can usually be cured by the older methods which, however, require more time in which to get results. A few of the patients who are treated by these older methods develop certain complications in the lower genital tract which, in most instances, are ultimately cured. In very rare instances patients treated by the older methods develop complications which involve the joints, the eyes, and other organs.

"A very small percentage of patients treated by modern methods experience slight discomfort while taking the medicine. This may consist of a tired sensation or a slight headache, but these symptoms never become serious if the patient is observed daily by the physician. Fever, skin rash, nausea and vomiting rarely occur but disappear rapidly when the treatment is stopped. Other reactions have been reported which involved the blood, joints, kidneys, liver, and nervous system, but these reactions have been so rare that the possibility of their occurrence is extremely remote.

"Before we can accept you as part of our group, it is necessary to obtain written permission from you.

" (place)  
(date)

"This is to certify that I have read, or have had read to me, and that I understand the above and foregoing statement.

Witness \_\_\_\_\_ (signature) "

\* \* \* \* \*

SUGGESTED PERMIT AND RELEASE

APPLICATION FOR INCLUSION IN STUDY ON  
CHEMICAL PROPHYLAXIS FOR GONORRHEA

"I, \_\_\_\_\_ # \_\_\_\_\_, \_\_\_\_\_, hereby  
(name) (age)  
voluntarily make application to \_\_\_\_\_  
(cooperating agencies)

for inclusion in the investigation on prophylaxis for gonorrhoea.

I have read, or have had read to me, and I understand the attached

"statement of procedure, which I have signed to evidence such fact.

"I hereby assume all risks of such tests and, acting for myself, my heirs, personal representatives, and assigns, do hereby release

\_\_\_\_\_ and their personnel, and all  
(institutions)  
others from all liability, including claims and suits at law or in equity, for any injury, fatal or otherwise, which may result from the tests.

Witnesses: \_\_\_\_\_ (signature)  
\_\_\_\_\_ (date)

OFFICER IN CHARGE

Consent is hereby given for the above named inmate to participate in the investigation of prophylaxis for gonorrhoea.

\_\_\_\_\_  
(signature of officer in charge) "

1.

MINUTES OF A CONFERENCE ON CHEMICAL PROPHYLAXIS

Held under the Auspices of the

SUBCOMMITTEE ON VENEREAL DISEASES at the NATIONAL RESEARCH COUNCIL

Washington, D.C.

November 18, 1942.

NOT FOR PUBLICATION  
WITHOUT PERMISSION OF  
NATIONAL RESEARCH COUNCIL

Present were Dr. J. E. Moore, Chairman, Subcommittee on Venereal Diseases, the following OSRD contract holders:

Dr. Frederick B. Bang, Rockefeller Institute, Princeton, N.J.  
Dr. Justina Hill, Johns Hopkins University  
Dr. Orlando Canizares, New York University, representing Dr. Frank Combes  
Dr. Harry Eagle, U. S. Public Health Service and Johns Hopkins University  
Dr. Geoffrey Rake, Squibb Institute for Medical Research, New Brunswick

the following interested physicians, present at the request of the Chairman, Subcommittee on Venereal Diseases:-

Dr. Charles M. Carpenter, Rochester, N.Y.  
Dr. Alfred Cohn, New York City  
Dr. H. O. Calvery, Food and Drug Administration, Washington, D.C.  
Dr. Murray Sanders, New York City  
Dr. N. E. Stokinger, Rochester, N.Y.

and in addition:-

Dr. T. R. Forbes, National Research Council  
Dr. S. J. Manchett, U. S. Public Health Service  
Dr. A. Rostenberg, Jr., and R. P. Horwick, Food and Drug Administration  
Lt. Col. T. E. Turner (MC) U. S. Army  
Maj. Robert Dyar (MC) U. S. Army  
Maj. G. W. Anderson, (MC), U. S. Army  
Capt. James M. Flood (MC), U. S. Army  
Lt. Harry Tebrock (MC) U. S. Navy.

The meeting was opened with a brief statement by the Chairman concerning its purpose. The Chairman remarked that recent surveys of OSRD contracts had indicated that investigators working along the same general broad lines seemed often to be unaware of the importance of their own particular problems to the major issue involved; were relatively unfamiliar with the type of investigation being pursued by other workers in the same field; and there thereby resulted an incoherent and uncoordinated effort which seemed likely to delay accomplishment of the major aim, namely, the development of chemical prophylactic agents more satisfactory than those now in use. The importance of the problem of chemical prophylaxis to the armed forces was stressed and the Chairman's remarks in these respects were verified and amplified by Lt. Col. Turner.

The various contract holders were each asked to outline their progress to date and, in brief summary, each reported as follows:-

Dr. Justina Hill has been unsuccessful in the production of gonococcal infection on the mucous membranes of the mouse, but has succeeded, and for the first time, in producing gonococcal septicemia by the intratesticular inoculation of gonococcus cultures without the use of mucin. She is now engaged in the effort to enhance the virulence of the strain in the hope that by doing so, local infection of mucosae may become possible. The method has already permitted a start at the evaluation of the time-dose relationship of oral sulfathiazole prophylaxis in mice, and this effort will be continued. Dr. Hill is also attempting to determine the factors which account for the extreme refractoriness of the genital mucosa of mice against gonococcal infection. Proceeding simultaneously in her laboratory are certain in vitro studies of the gonocococidal effect of various substances, including arsenicals supplied by Doctors Eagle and Rake.

Dr. Murray Sanders, who is not at present an OSRD contract holder, reported that he has studied the local application of sulfanilamide ointments in normal human urethras with respect to their irritating properties and their absorption. At the moment his time is fully occupied with other projects in the virus field, but he hopes that it may be possible for him to return to the field of mechanical prophylaxis.

Dr. Thompson, who unfortunately was not present through a secretarial error in failing to send him an invitation, is engaged in a systematic study of experiments with various emulsions, wetting agents, etc., perhaps useful as vehicles for the solution or suspension of chemotherapeutic agents.

Dr. Cohn, who is associated with Dr. Thompson's contract, reports that he has treated certain human patients with acute anterior gonorrhoeal urethritis with sulfonamide ointments, with results which appear to be encouraging for the future prosecution of this type of study.

Dr. Bang has studied the effect of various chemical agents on gonococcal infection of the chorio-allantoic membrane in the chick. Of the sulfonamides investigated, sulfathiazole is the most effective, but certain arsenical compounds, including an arsenobenzene-sulfonamide preparation, supplied to him by Dr. Rake, mapharsen, clorarsen, and sulpharsphenamine are even more effective than sulfathiazole. Dr. Bang plans to terminate his work in about a month, but the importance of the technique is such that the consensus of the Conference was that it would be desirable for the technique and, if possible, the technician in Dr. Bang's laboratory to be taken over in the laboratory of Dr. Hill or of some other worker.

Dr. Rake has been engaged in a study of the viricidal effect of various compounds against the virus of lymphogranuloma utilizing egg yolk inoculation. He has developed a method of separating in vitro and in vivo effect. He has found that sulfonamides have no in vitro activity, but that they are effective in vivo. The most effective substance tested has been an arsenobenzene-sulfanilamide compound ("434") which is effective against the virus of lymphogranuloma in a concentration

of 1 mg. per 100 c.c. of diluent against 1 million lethal doses of the virus. Dr. Rake is now engaged in the effort to find vehicles in which arsenicals or other compounds can be dissolved or suspended, and which will be free of irritating properties, will have no effect on the toxicity or therapeutic activity of the added drug, may have a possible additive effect from the vehicle itself, and which will have enhanced penetrating properties.

Dr. Rake reports that guinea pigs are susceptible to inoculation with lymphogranuloma by the scratch method and undertakes to determine the local effect of various chemotherapeutic agents in preventing such infection.

Dr. Canizares, reporting for himself and Dr. Combes, has been trying the effect of various chemotherapeutic agents in the prevention of auto-inoculated chancroid, and has determined that sulfathiazole in a simple petrolatum base is effective, while soap and water and calomel ointment are not. He is now trying the effect of oral sulfathiazole. He has not yet tried arsenicals but agrees to do so.

Dr. Eagle reports that he has studied the effect of soap and water and of calomel ointment in the prevention of syphilis in experimental animals. Soap and water is effective in vitro, but not in vivo. Calomel ointment in the dosage used in man (i.e., approximately 20-25 mg. per pilo) is effective in preventing chancre formation, but its effect in actual prevention of symptomless infection has not yet been determined.

The possibility of human experimentation in gonorrhoea was discussed by Drs. Carpenter and Cohn. The former has already made contact with the Prison Commission of Georgia, and the latter with the Commissioner of Health of New York City in conversations which seem to indicate that there is a possibility of arranging such experiments in prison inmates. It was agreed that the Chairman of the Subcommittee on Venereal Diseases will attempt to obtain official governmental backing for such human experimentation through the Surgeons General of the Army, Navy, and Public Health Service, the Committee on Medical Research, and OSRD; and that if these efforts are successful and approved by the appropriate authorities, representations may be made to the appropriate State authorities of Georgia, New York, and perhaps other States by an official representative of the National Research Council with the idea of expediting the accomplishment of the study under the direction of Drs. Carpenter, Cohn, or other interested persons. It was agreed that if human experimentation could be arranged, the initial effort should be devoted to a delineation of time-dose relationships of oral sulfathiazole, and that the local application of chemotherapeutic substances might properly await better information concerning vehicles, penetrants, etc.

There then ensued a general discussion of the importance of a systematic study of vehicles, emulsion bases, penetrants, wetting agents, etc. It was agreed that up to this point the several investigators involved have been dealing individually with one or another pharmaceutical house, and that vehicles for the solution or suspension of chemotherapeutic substances have been largely empirically selected without adequate knowledge of their relative merits. The Chairman pointed out that

for this reason Dr. H. O. Calvery, Chief Pharmacologist of the Food and Drug Administration, had agreed to undertake a systematic study of these agents and had applied for an OSRD contract for this purpose. Dr. Calvery then spoke briefly to the points and expressed his entire willingness to cooperate with other members of the group engaged in prosecution of one or another aspect of the general problem of chemical prophylaxis.

There also ensued a considerable discussion as to whether other investigators not as yet associated with these studies might not be purposely drawn into them through the Subcommittee on Venereal Diseases. Among those suggested for the Chairman to approach were Dr. Oscar Cox of Boston, Dr. Phillip Miller of Chicago, Dr. Austin Deibert, U.S. Public Health Service at Hot Springs, Arkansas, and Dr. A. L. Tatum, Madison, Wisconsin, all of whom have certain facilities likely to prove of value in the laboratory or clinical testing of chemotherapeutic agents, particularly against gonorrhea.

It was likewise suggested that some time might be saved with regard to chancroid if improved culture methods could be developed or utilized. In this respect the Chairman was authorized to get in contact with Dr. Greenblatt of the University of Georgia. The Chairman was likewise authorized to approach Dr. Katharine Anderson of Vanderbilt University regarding the suitability of her method of infection of chick embryos with chancroid, in a study of chemical prophylaxis.

The question was also considered of the desirability of further studies as to the possible sensitizing effect of the sulfonamides administered either locally or orally. No definite decision was reached as to investigators to be approached in this field. It was said that Dr. Harrison F. Flippin had had certain experiences in this connection with the prolonged treatment of nurses at the University of Pennsylvania with sulfathiazole for the common cold. The Chairman was directed to write Dr. Flippin and also to consult others interested in the field of sulfonamide therapy, to determine whether such investigation could be organized under the auspices of the Subcommittee on Venereal Diseases.

Finally, there was general discussion of the desirability of coordinative effort in the field of chemical prophylaxis. The Conference agreed to the appointment of a committee to draw up an organized plan of attack and to indicate to present or potential OSRD contract holders the most immediate profitable lines of investigation for themselves to follow. The Chairman appointed himself as Chairman ex officio of this committee, and as its members Doctors Harry Eagle, Geoffrey Rake, and H. O. Calvery.

The meeting then adjourned.

Minutes of Meeting at Duke Medical School, Durham, North  
Carolina, on Friday, September 4th, 1942.

From Dept. of Experimental Surgery: Doctors Beard, Sharp and assistants.

From Dept. of Biochemistry: Doctor Neurath and assistants.

From Dept. of Syphilis: Doctors Callaway and Craig.

From Subcommittee on Venereal Diseases: Doctor Fagie.

The organization of the projected study on the identification of the serum protein fractions with which the various types of reagin are associated was discussed in detail. Doctors Neurath and Beard agreed that the most direct method of approach would be to obtain protein fractions by salting out at low temperatures, to use the Tiselius as a guide to the purity and concentration of the fractions obtained, and perhaps for their final purification. Doctor Neurath would be responsible for the salting out, and Doctor Beard's department would do the Tiselius separations. The fractions obtained would be submitted to the routine serologic laboratory of the hospital. Unfortunately, the only serologist available is the one who performs the routine Wassermann and flocculation tests; but an additional worker in the laboratory would free him for the serologic study of the protein fractions. It was decided that at least in the early phases of the work the group would concentrate only on those human sera giving definite reactivity, i.e., syphilitic sera, normal human sera giving clear-cut biologic false positive reactions, and the falsely positive sera of persons with intercurrent infections. Depending on the early results, the group would then consider a study of animal sera, and the identification of the reagin present in minute amounts in all normal human sera. The latter study presents a special problem because the serologist is not familiar with the special technics that study would entail.

It was made clear that the present conversations do not represent a commitment of either the subcommittee or by the Committee on Medical Research. On their own responsibility, the group at Duke has already begun work leading to the identification of the reagin in syphilitic serum. In the near future Doctors Beard and Neurath, as joint responsible investigators, will submit a joint proposal to the Subcommittee on Venereal Diseases for a contract, the amount requested to be used as a contingent fund and for the salary of a serologist.

copy in room 1.D.      Index 1

Minutes of Luncheon Meeting at Rockefeller Institute  
of Medical Research, Wednesday, Sept. 2, 1942

From Rockefeller Institute:      Doctors Shedlovsky and Longworth

From Columbia University:      Doctors Heidelberger, Kabat and Moore

From Venereal Disease Research Laboratory, Stapleton, N.Y.:      Dr. Harris

From Lederle Laboratories:      Doctor Weil

From Subcommittee on Venereal Diseases:      Doctors Moore, Mahoney and Eagle

Confirming the conclusions of a previous meeting in Washington, it was the consensus of Doctors Shedlovsky, Longworth and Moore that the most promising method of fractionating serum protein for serologic study would be salting out with varying concentrations of  $(NH_4)_2SO_4$  at low temperatures, followed by electrophoresis in the Tiselius apparatus, and that the smaller cell would give a sharper separation than the large cell. This would also simplify the problem of serum collection.

In the absence of Mr. McInnes, the Rockefeller group were not able to assure their participation in the projected study; but even with his approval such participation would be feasible only if a skilled worker were provided. Doctor Longworth knew of no such person immediately available, but agreed that Doctor Bernard Davis, who has built an apparatus which is a duplicate of his own, would be entirely acceptable if he were made available for this study by the U. S. Public Health Service. No agreement was reached as to who would be the responsible investigator at the Rockefeller; and since Doctors Longworth and Shedlovsky already have prior O.S.R.D. contracts, it was tentatively suggested that Doctor Rothen of the Rockefeller staff might serve in that capacity.

As a second choice, should Doctor Davis not be available, it was tentatively agreed that Doctor Moore at Columbia Medical School would undertake the problem of separating the serum fractions, provided that technical assistance could be made available. Doctor Moore would not need a worker capable of independent investigation, such as Doctor Davis, but would require only a skilled technical assistant.

As a third possibility it was suggested that the entire study, both the separation of the serum fractions and their serologic study, might perhaps be organized at the Lederle Biological Laboratories.

Dr. Mahoney agreed to make available adequate amounts of the several types of sera scheduled for study to whichever laboratory would undertake the physical and chemical manipulation.

It was emphasized by Doctor J. E. Moore that he could make no present commitment for either his committee or the Committee on Medical Research; and it was agreed that the first step leading to the organization of the study would be to ascertain, on Surgeon General Parran's return about September 25th, Dr. Davis' availability.

RESTRICTED

MINUTES OF  
CONFERENCE ON BIOLOGIC FALSE POSITIVE SEROLOGIC TESTS  
FOR SYPHILIS  
HELD AT THE NATIONAL RESEARCH COUNCIL AUGUST 13, 1942.

This conference was called by authorization of the Subcommittee on Venereal D seases at its meeting on July 24, 1942, subsequently approved by the Committee on Medicine. Present at the conference on August 13th were the following:

Dr. Edmund J. Cohn, Harvard University  
Dr. Duncan MacInnes, Rockefeller Institute for Medical Research  
Dr. Elvin Kabat, College of Physicians and Surgeons, Columbia University  
Dr. Forrest Kendal, Welfare Laboratories, Welfare Island, New York  
Dr. J. Murray Luck, Stanford University  
Dr. Harry Eagle, U.S. Public Health Service, Johns Hopkins University

and from the Subcommittee on Venereal Diseases Doctors Stokes, Mahoney, and Moore.

The Chairman, Dr. Moore, initiated the conference by reading certain statements dealing with the importance of biologic false positive serologic tests to the Armed Forces. There was then read a tentative agenda which follows:-

"Agenda For Conference On Differentiation Of Various Types of Reagin."

"Normal human serum occasionally contains small amounts of a substance resembling the reagin of syphilitic serum in its reactivity with Wassermann and flocculation antigens. A similar reactivity is frequently observed in the course of many febrile diseases other than syphilis. The mistaken diagnosis of syphilis resulting from this anomalous reactivity is a matter of growing concern in both the civilian population and the armed forces.

"No simple method of distinguishing between these three types of reagin (four if one includes that encountered in the serum of many animal species) has yet been developed. The reagin of syphilitic serum is associated with the globulin fraction (whether alpha, beta or gamma, is unknown), and is itself apparently protein in nature. Not even this much is known of the other types of reagin. The present conference has been called to discuss the practicability of determining the fraction or fractions of serum protein with which the several types of reagin are associated, in the hope that different and perhaps readily separable fractions are concerned in the various types of reactivity.

"Electrophoresis in a large-scale Tiselius apparatus has been suggested as the simplest available method of fractionating the serum protein. Are other methods (e.g., salting out, ultracentrifugation) so inefficient in comparison that they may be, at least temporarily, disregarded; or does some approach other than electrophoresis offer promise?

"2. Whatever method is agreed to be the first line of attack, what amounts of each type of reactive serum (animal, normal human, syphilitic human, and from patients with diseases other than syphilis) would be necessary to per-

"mit the separation of the known fractions? The yield need be only enough to permit adequate serologic study, e.g., 100 mgs. of each fraction for purposes of orientation.

"3. Which laboratory has the necessary equipment, not already in constant use, to undertake the fractionation of the various types of serum? Would present personnel suffice, or would an additional worker be necessary?

"4. The collection of adequate amounts of animal serum and syphilitic serum presents no difficulties. The provision of large amounts of serum from patients, both normal and febrile, who give biologic false positive tests for syphilis, will offer greater difficulty, and plans for collection should be made.

"5. The fractions as isolated will have to be studied by a competent immunologist with respect to their reactivity with Wassermann and flocculation antigens. Must that work be done in the same laboratory; or can the fractions be safely shipped to some outside laboratory without danger of bacterial contamination or denaturation? In either case, who will undertake the study of the separated fractions? The work can certainly not be entrusted to the average serologic technician; and most competent workers have prior commitments. The laboratories of Doctors Kahn, Lund, or Mahoney may perhaps be considered. "

The subsequent discussion revolved around these agenda.

The conference agreed that the methods of approach suggested in the agenda were entirely feasible. Considerable discussion ensued as to the relative merits of electrophoresis by the use of the Tiselius apparatus and of the chemical fractionation of human plasma as carried on in Dr. Cohn's laboratory.

The Chairman is frank to admit that much of this discussion was over his head and that the details of it will be provided in a memorandum subsequently to be supplied by Dr. Harry Eagle who acted as the Chairman's secretary.

Agreement was reached on several points, however, as follows:-

1. It is desirable to attempt to define with which fraction of globulin reagin, whether syphilitic or otherwise, is associated. Preliminary efforts to do this should be carried out with a Tiselius apparatus which permits not only identification but also separation of the globulin fractions concerned.

2. Involved in such a problem is a group effort including clinicians (for an adequate supply of sera from persons with syphilis and with biologically false positive serologic tests), physical chemists or immunochemists, for the separation and identification of the protein fraction containing this reagin, and serologists for its subsequent study.

3. Studies of this nature should be carried on in two or three laboratories simultaneously.

One of these laboratories should be at Duke University, the problem to be attacked by Dr. Hans Neurath in association with Dr. James E. Beard and with a responsible clinician and serologist. Dr. Neurath was communicated with by telephone by Dr. Wilbur Davidson, and signified the willingness of his laboratory to participate.

The second laboratory should, if possible, be located in New York. It was suggested that here the ideal set up would be to obtain Dr. Michael Heidelberger as the responsible investigator, to associate with him Dr. Elvin Kabat, and from the serologic standpoint Dr. John F. Mahoney; and also to associate with him as consultants Doctors MacInnes and Foster Kendall. The Chairman of the Conference was authorized to interview Dr. Heidelberger, and to arrange for a further group discussion at the Rockefeller Institute in New York at a meeting tentatively set for Wednesday, September 2nd. Unfortunately, Dr. MacInnes could not be present at this meeting but at his suggestion the Chairman has communicated with his associate Dr. Theodore Shedlovsky, with the request that such a meeting be arranged. It is tentatively planned to have present at that meeting Doctors Heidelberger, Kabat, D. H. Moore, Mahoney, Ad Harris, Forrest Kendall, Walther Gobel, Harry Eagle, and J. E. Moore.

It was likewise agreed that it might prove to be desirable to set up a similar group at Stanford University under the direction of Dr. J. Murray Luck. Dr. Luck, in turn, agrees to consult with his associates on his return to California the first week in September, and to notify the Chairman, Subcommittee on Venereal Diseases, as to what extent, if any, his group can cooperate in this problem.

4. It was further agreed that close coordination between participating laboratories would be of the utmost importance; that the general supervisory control of such a study should be placed in the hands of a single person; that this person should be Dr. Harry Eagle.

At 1:00 P.M. the meeting adjourned.

"Copy not corrected by Dr. Eagle"

Minutes of Meeting on Biologic False Positive Tests for Syphilis:

Thursday, August 13, 1942.

Present:

- |                |                 |
|----------------|-----------------|
| J. E. Moore    | Duncan McInnes  |
| John H. Stokes | Murray Luck     |
| J. F. Mahoney  | Henry Eagle     |
| Elvin Kabat    | Forrest Kendall |
| E. J. Cohn     |                 |

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All present agreed that the identification of the protein fractions with which the various types of reagin are associated may offer an approach to their possible differentiation. It was further agreed that electrophoresis provided the simplest method of orientation, although a combination of physical and chemical methods might ultimately be necessary. The dissociation of reagin from lipoid-reagin floccules by the methods of Witebsky and of Bier and Schraft was suggested by Dr. Kabat as possible alternative approach.

Of the four laboratories represented at the conference in which a Tiselius apparatus is available, that of Dr. Cohn is now engaged in the large scale fractionation of serum and would not be immediately available for the projected study. (Fractions of normal serum could however be supplied for study). Each of the other three laboratories (Dr. McInnes at Rockefeller; Dr. Kabat at Columbia; Dr. Luck at Stanford) is now engaged on other projects, and their collaboration could not be assured. In each case, personnel would be a limiting factor; and whichever laboratory were to undertake the study, provision of a competent worker would probably be a necessary condition. Dr. Bernard Davis, now a commissioned officer of the U. S. Public Health Service, stationed at the National Institute of Health, was suggested as having the necessary skill and ability. It was agreed that Dr. Moore would take up with Surgeon General Parran the possible availability of this officer.

Commercial houses which are participating in the collection and processing of serum for transfusion purposes (Lederle, Squibb, Lilly, Upjohn, Sharp & Dohme) were suggested as a ready source of Wassermann-positive serum.

It was agreed that the serologic study of the fractions obtained on electrophoresis should be carried out in the same laboratory, or at least, in the same city. The desirability of having the entire study, both physical separation and serologic characterization, duplicated in two different laboratories, with mutual cross-checking of serum fractions, was stressed by several of the conferees. It was further agreed that Dr. Herbert Lund be asked to participate in the study, and particularly in relation to the serologic reactivity of fractions obtained from normal serum.

The possible participation of Duke University Medical School was suggested by Dr. Wilbur Davison. A Tiselius apparatus is known to be available; a large syphilis clinic assures a supply of the various types of sera; and there is reason to believe that a competent serologist would be available.

MEMORANDUM  
FOR THE  
NATIONAL RESEARCH COUNCIL

Because of the number of laboratories which will be involved in this study, it was decided, subject to the approval of Surgeon General Purran, that Dr. Harry Eagle would be asked to coordinate their activities.

The following steps were agreed upon as leading to the early organization of the projected study:

a) Dr. Luck to investigate the possible collaboration of the group at Stanford.

b) Columbia University to be one of the participating laboratories, the serum fractions there obtained to be sent to Dr. J. F. Mahoney (Venereal Disease Research Laboratory - Staten Island) for serologic study. A meeting will be held on Wednesday, September 2nd, at the Rockefeller Institute to make more definite arrangements (Doctors Theodore Shedlovsky, Michael Heidelberger, Elvin Kabat, Dan H. Moore, J. E. Moore, J. F. Mahoney, Ad Harris, Forrest Kendall and Walther Goebel to be present).

c) Dr. Eagle to go to Duke University immediately afterward to confer with Doctors Beard, Neurath, Perlzweig, and Callaway as to their possible participation.

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.

NOT FOR PUBLICATION  
WITHOUT PERMISSION OF  
NATIONAL RESEARCH COUNCIL

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

July 7, 1942.

These minutes appear as Exhibit A appended to the

minutes of the July 24th meeting of the Subcommittee  
on Venereal Diseases.

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Very sincerely yours,

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

Dr. J. E. Moore  
Baltimore, Maryland.

Dear Doctor Moore:

NOT FOR PUBLICATION  
WITHOUT PERMISSION OF  
NATIONAL RESEARCH COUNCIL

July 13, 1942.

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. Wood, 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:

Conference:

Dr. Margaret Barnard, New York City Health Department; Dr. Mary Fisher, Vassar College, Poughkeepsie, N.Y. Dr. Ernest Groves, University of North Carolina,

MINUTES OF A CONFERENCE ON THE PREVENTION OF VENEREAL DISEASE  
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NATIONAL RESEARCH COUNCIL

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  
Baltimore, Maryland.

FOR PUBLICATION  
BY PERMISSION OF  
NATIONAL RESEARCH COUNCIL

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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. Skull, W. A. Brunfield, 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. Shrouts from the Office  
of the Surgeon General, and Miss Elizabeth P. Taylor representing Miss  
Mildred McAfee, Civilian consultant Navy Women's Reserve Corps, Audio-  
Productions Inc. 630 N

Also present were Miss Roberta Zechiel, 630 Ninth Avenue, New York, a script  
writer for Navy motion pictures, and Mr. Morris Ernst, the legal adviser  
of the American Birth Control League.

The discussion of this conference hinged around a tentative agenda herewith  
appended as Exhibit A.

The Chairman of the conference opened the discussion by reading certain docu-  
ments relative to the experience of the British Women's Auxiliary Services, parti-  
cularly 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 difficul-  
ties 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 were 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 guessed at 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 expose themselves, regardless of temptation; and 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 WAAC the guess was hazarded that these proportions would 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 exposed under similar circumstances 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 then proceeded to a discussion of the relation of the venereal disease problem to the problem 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 WAAC 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 services to be available to the WAAC seemed to the conference to be of import-

ance. (In this connection Col. Tasker stated that the policy of the WAAC would be to commission women physicians directly as officers in that service, since authority did not exist to commission such women physicians 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 roll 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 WAAC, and to this end it was recommended:

THAT A SPECIALLY TRAINED MEDICAL OFFICER BE PROVIDED TO HEADQUARTERS WAAC THROUGH THE DIVISION OF PREVENTIVE MEDICINE, OFFICE OF THE SURGEON GENERAL UNITED STATES ARMY, THIS OFFICER TO FUNCTION ADMINISTRATIVELY UNDER THE WAAC, 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 THE WOMEN AND RELATED PROBLEMS, INCLUDING VENEREAL DISEASE CONTROL.

It was requested at this point by Capt. Stephenson and 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.

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 WAAC constitute a special group. They are as much in need of educational effort as the rest of the 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 realistic information 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 was 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 committee. It is planned that this lecture, covering a 2-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.)

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 probably differ in character, according to the type of personnel to which it is addressed; e.g., medical officers without special training in the field, 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 approaching uniformity in methods of educational approach, this conference recommended that:

A SUBCOMMITTEE BE APPOINTED BY THE CHAIRMAN TO PREPARE FOR THE USE OF THE WAAC 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 Dr. Mary Fisher, Chairman, Ernest Groves, Raymond Squier, and Bertha Shafer. This subcommittee will meet in New York 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 largely now 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 Film Council Repository.

As to plans of the Army and Navy for the education of women by motion pictures, it was brought out by Col. Tasker, speaking for the Army, that such a film was proposed but 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 prophylaxis, and especial 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 A DESIRABLE PART OF THE EDUCATIONAL TECHNIQUE OF FEMALE PERSONNEL OF THE WAAC: THESE MOTION PICTURES SHOULD INCLUDE THE MAIN ESSENTIAL POINTS ALREADY OUTLINED FOR THE PROPOSED NAVY PICTURE: AND, IF POSSIBLE, IN ORDER TO MINIMIZE EXPENSE AND TO ENSURE UNIFORMITY OF EDUCATIONAL EFFORT ARMY AND NAVY SHOULD COLLABORATE IN THE PRODUCTION OF SUCH A MOTION PICTURE TO BE UTILIZED BY THE WAAC AND BY THE ANALOGOUS AUXILIARY 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 in New York 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 American Birth Control League, spoke in effect as follows:

Mast, P.

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 3 years, 1870-1873, practically all of 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, and 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 Court, 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. 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 of 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 that 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 pussy-footing. Courage in presentation will, he believes, meet with public approval.

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 WAAC through the several educational techniques to be outlined by Dr. Fisher's sub-group.

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, 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:-

CONDOMS SHOULD BE MADE AVAILABLE TO THE PERSONNEL OF THE WAAC AT COST, PREFERABLY THROUGH SLOT MACHINES RATHER THAN BY DISTRIBUTION OR PURCHASE THROUGH POST EXCHANGES; AND THAT SUCH SLOT MACHINES, IF APPROVED, SHOULD 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 WAAC 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 WAAC 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. Insker as to the disciplinary control of female personnel with regard to evening, over-night, and week-end leaves. Col. Insker 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 WAAC 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 WAAC 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 WAAC 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 WAAC 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 WAAC, 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 is being made on all officer candidates, and will be made on all enlisted personnel, married and unmarried. This latter procedure will exclude obvious cases of gonorrhoea and serious gynecological disorders. In effect, therefore, the WAAC 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 WAAC 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 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 difficulty, and it was therefore recommended that:-

PERIODIC MEDICAL INSPECTION FOR VENEREAL DISEASE OR PREGNANCY BE NOT UTILIZED  
IN THE WAAC.

\* \* \* \* \*

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 THE UNDUE SEGREGATION OR STIGMATIZATION IN THE  
TREATMENT OF VENEREALLY INFECTED WOMEN PERSONNEL OF THE WAAC.

\* \* \* \* \*

The question was raised as to the disposition of pregnant women. It was said by Col. Tasker that regulations of the WAAC 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 "discharged without honor" and that she may not subsequently re-enroll. The question was further raised as to the distinction in the lay mind between "discharged 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 WAAC 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 "DISCHARGE WITHOUT HONOR". 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 WAAC it was pointed out that the environmental change to which women from civilian life would suddenly be subjected would almost surely bring about many menstrual irregularities and periods of prolonged amenorrhea; and that these menstrual irregularities, or 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 FRIEDMAN TESTS FOR PREGNANCY ON FEMININE PERSONNEL WHEN INDICATED.**

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

Respectfully submitted,

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

From:  
J.E. Moore

W. Cushing

APR 15 1942

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CONFERENCE ON BIOLOGIC FALSE POSITIVE  
SEROLOGIC TESTS FOR SYPHILIS

At the suggestion of the Subcommittee on Venereal Diseases, and with the approval of the Committee on Medicine and the Division of Medical Sciences, National Research Council, there was held in Washington on March 26, 1942, a conference on the subject of biologic false positive serologic tests for syphilis. Present were Doctors Moore and Stokes of the Subcommittee on Venereal Diseases; the following invited experts: Dr. Harry Eagle (U.S. Public Health Service) Johns Hopkins University, Dr. Reuben Kahn, University of Michigan, Dr. Joan Mahoney, U.S. Public Health Service, Venereal Disease Research Laboratory, Stapleton, Staten Island, Dr. Herbert Lund, Western Reserve University, Cleveland, Dr. B. S. Kline, Western Reserve University, Cleveland, Dr. John A. Kilmer, Temple University, Philadelphia and Dr. W. A. Hinton, Boston, Mass. Also present were Captain Stephenson and Commander Grieves, U.S. Navy, Colonel Callender, Lieut. Col. Kimbrough, Lieut. Col. Prentiss, Lieut. Col. Turner, Major Gordon and Major Hogan, U.S. Army; Doctors Wushing and Larkey, National Research Council, and Dr. Walker, Committee on Medical Research.

The Chairman opened the discussion by reading the following introductory statement:

This meeting has been called at the suggestion of the Subcommittee on Venereal Disease, National Research Council, in order to consider possible methods of approach to the solution of the problem of biologic false positive serologic tests for syphilis, of importance to the Armed Forces and civilian population alike.

Some of the present group of serologists have already contributed to certain details of the problem and it is clear that further work along lines already initiated should be continued.

It is desired, however, to develop a broader plan of attack which may lead to a more rapid solution of the fundamental issues involved. You have been invited to attend this conference to discuss the desirability and feasibility of certain definite avenues of study listed below: to suggest whether any one or several of you or other investigators in the country not present at this meeting, are specially qualified, equipped and willing to undertake such studies; to advance suggestions for other studies not herein included; to determine if various parts of the problem are allocated, whether funds in addition to those already available are necessary to bring such studies to completion; and to discuss the desirability of application for such funds by interested investigators to the Office of Scientific Research and Development through the Committee on Medical Research.

It is emphasized that war makes certain problems of which this is one of more immediate practical importance than in more normal times. Group effort is now more desirable than leisurely individual effort. Ideas should be pooled and work shared in an effort at rapid solution. New avenues of approach to this or other problems suggested by an investigator need not be jealously guarded for fear of loss of the individual glory to be gained by priority. If new and valuable ideas evolve from any person at this meeting, the opportunity of first

study of them will of course be his. If his ideas develop favorably and if his result is of such a nature as to require confirmation, some one else may be asked to undertake similar studies.

In general, if it is agreed by this meeting and subsequently by the Subcommittee on Venereal Disease that the study of this particular problem be undertaken, it should be viewed as an entity with several integral parts to be prosecuted cooperatively under the general auspices of the Committee on Medical Research with frequent interchange of ideas and information between the several investigators engaged.

It is suggested that the problem be discussed under the following headings:

1. The Kahn Verification test.
2. Spirochetal complement fixation tests.
  - a. Development of improved and reproducible antigens.
  - b. The further use of such antigens in conditions other than syphilis.
  - c. The use of such antigens in normal animals known to give false positive tests with ordinary tissue extract.
3. Further study of Lund's technic, especially in normal persons and in conditions other than syphilis, perhaps as a quantitative measure of the degree of false reactivity and the relationship of reactivity of most normal sera to that shown by sera from syphilitic and nonsyphilitic persons giving positive diagnostic tests for syphilis.
4. Differential adsorption by filters of normal and syphilitic reagin.
5. Chemical identification and possible differentiation of substances in tissue extracts reacting with normal and syphilitic reagin.
6. Nature of substance in nonsyphilitic serum responsible for reactivity with tissue extracts.
  - a. Effect of antisyphilitic treatment in seropositive animals.
  - b. Does nonsyphilitic reagin bear any relation to the substance responsible for rouleaux formation and red blood cell sedimentation.
  - c. Does this substance produce false positive results with various nonspecific serologic techniques.

In further scientific amplification of this statement the Chairman also read the following statement:

The attention of serologists and syphilologists alike has recently focused on the reliability of the serodiagnostic tests for syphilis. It has been known for many years that certain conditions other than syphilis may cause the transitory appearance of positive serum tests for that disease; and the possibility of such false reactions enjoins caution in the interpretation of positive Wassermann or flocculation tests observed for the first time during, or immediately after, some intercurrent infection. It is now becoming increasingly clear that similar biologic false reactions may be observed in the absence of any complicating disease. Their incidence in clinically normal adults is a moot question; but whether they occur once in every 1,000 or once in every 4,000 persons, they may constitute a significant proportion of the positive tests encountered in routine serologic surveys. Moreover, to the individual concerned, their differentiation from positive reactions due to syphilis is of crucial importance.

It has been demonstrated by at least four different groups of observers that many normal human sera contain traces of a substance which, like the reagin of syphilitic serum, causes the aggregation of the tissue lipoids used as "antigen" in the several diagnostic tests for syphilis. Perhaps because of the different techniques used for the detection of this reactivity, estimates as to the proportion of human sera in which it may be demonstrated vary from 1.3 to 98 per cent. Unlike the case of animal sera, many of which give frankly positive and even high-titered diagnostic tests for syphilis in the absence of that disease, the reactivity of normal human sera with flocculation antigens is usually only minimal in degree, requiring refined techniques for its demonstration, and is usually not apparent in the diagnostic tests. It is possible that the occasional human serum which gives false positive diagnostic tests contains an excess of this normal factor, ordinarily present only in traces. It is equally possible that such biologic false reactions bear no relationship to the normal flocculating activity of human serum, and are due to an entirely different substance.

In either case, the point of practical significance is whether the reactivity of non-syphilitic human sera can be distinguished from that of syphilitic sera. Can a test be devised to distinguish between syphilis reagin on the one hand, and either "normal" reagin or that elaborated in the course of intercurrent infections on the other hand? Two procedures which may be of value in that direction have recently been reported. One is the so-called "verification" test developed by Kahn and his associates, which is based on their finding that animal sera and those of non-syphilitic human beings react with a tissue

lipoid "antigen" more strongly at 1° C. than they do at 37° C., while the reverse is said to be true of syphilitic sera. The relative degree of flocculation observed at these two temperatures may therefore be used to differentiate "syphilitic" from "biologic" types of reaction. However, the validity of the procedure has not yet been confirmed in other laboratories. Chargin and Rein have not found the procedure as performed in Kahn's own laboratory to be reliable. Some sera from known cases of syphilis were found to give the biologic type of reaction, while some non-syphilitic sera were found to give the syphilitic type of reaction. Moreover, repeated specimens from the same individual gave conflicting results. For the present, the procedure must therefore be considered to be in the experimental stage, and is not yet a test on which to base a definitive opinion as to the significance of a positive result.

The second laboratory procedure which may prove to be of value in differentiating biologic false positives from positive tests actually due to syphilis is the spirochetal complement fixation test developed by Gaeghtens, on which there is an extensive bibliography in the German literature, and which has been studied in this country by Eagle and his associates. Their published work to date is based entirely on the proprietary preparation "Palligen", which purports to be a washed suspension of cultured Spirochaeta pallida (Reiter strain), and which is unfortunately no longer available in this country. Using that preparation, several workers have found this procedure to be more reliable than ordinary flocculation or Wassermann tests with tissue antigens in differentiating leprosy and syphilis, but no more reliable than those tests in differentiating malaria and syphilis. Although Kolmer and his associates have found their own preparations of cultured spirochetes to be wholly unreliable in the serum diagnosis of syphilis, giving as high as 25 per cent false positive reactions with non-syphilitic sera, those results are so completely at variance with the published data on the proprietary preparation "Palligen" that it is well to withhold judgement.

This much however can be said. Even if it should be possible to prepare suspensions of cultured spirochetes reacting as sensitively as do tissue extracts with syphilitic serum, and further, even if such spirochetal suspensions were found to give negative tests with a considerable proportion of sera which give biologic false reactions with tissue antigens, such suspensions would not be the final answer to the present problem. Since they are not actually suspensions of Spirocheta pallida, they presumably owe their reactivity to a cross-reaction with that organism, and such cross reactions might well extend to other diseases. The apparent reactivity of these suspensions with malarial serum is a case in point. At best, such suspensions will be another imperfect tool permitting the possible differentiation of some, but by no means all, biologic false reactions from those due to latent syphilitic infection.

Fundamental studies on the nature of the substance responsible for these biologic false reactions are clearly indicated. At the outset, it may be advisable to distinguish between four types of reagin, some of which may ultimately prove to be identical: (a) the flocculating factor present in minute traces in many normal human sera; (b) the "reagin" present in the occasional human serum in amounts sufficient to give a positive or doubtful diagnostic test; (c) the "reagin" elaborated in the course of such non-syphilitic diseases as leprosy, malaria, cowpox, and infectious mononucleosis, to mention only a few; and finally, (d) the "reagin" elaborated in the course of syphilitic infection. Quantitative measurement alone does not permit their differentiation. Although most sera giving biologic false reactions are barely positive, this is not necessarily the case, as high titered reactions may be observed; while sera from indubitable cases of syphilis, early as well as late, may give extremely low-titered or doubtful results. The technical procedure recently proposed by Lund offers a promising approach to the quantitative measurement of the reagin-like factor in normal sera.

Corollary to the possible chemical identification of the serum components responsible for these several types of reactivity, studies should be carried out on the fractionation of the crude tissue extracts used as "antigen" in the Wassermann and flocculation tests: for it is possible that the different types of "reagin" react with different substances in those extracts.

I. In accordance with the agenda given in the Chairman's opening statement the Conference proceeded to a consideration of the Kahn verification test. Dr. Kahn made a long statement concerning this test which was then further discussed by others. It was pointed out that in a publication by Chargin and Rein (Arch. Dermat. & Syph. 44: 1031, 1941), and in a subsequent as yet unpublished paper by Rein, the Kahn verification test does not always give a negative type of verification reaction in persons presumably free from syphilis; is not always repeatedly verifiable in the same patient; does not consistently mean that the syphilitic type of reaction indicates syphilis; and that persons with biologic types of verification reaction do not always, or necessarily frequently, give false positive standard serologic reactions.

It was likewise pointed out by Dr. Kline and also in the unpublished manuscript by Dr. Rein, that the Kahn "verification phenomenon" may depend on certain impurities in the antigen rather than on an actual biologic phenomenon.

It was nevertheless agreed that the Kahn verification test offered an avenue of approach to the problem of biologic false positive tests and that investigative work with this test should continue. Of the several serologists present at the meeting, only Dr. Kahn appeared to be equipped for further intensive study of this phenomenon, the other serologists indicating

that their laboratories were otherwise occupied.

In respect of the Kahn verification test a proposal for contract by Dr. Kahn to the Office of Scientific Research and Development is already pending before the subcommittee on Venereal Diseases.

II. The spirochetal complement fixation test was next discussed and it was agreed that this, too, gave some promise of becoming a valuable aid in the differentiation of the biologic false positive tests from those caused by syphilis. It was further agreed that work with this test should continue in the two laboratories which have already undertaken it, i.e., those of Dr. Eagle and Dr. Kolmer. The other serologists present felt that their own laboratories were otherwise occupied and they had no suggestions for further studies with spirochetal antigen. There was no suggestion that O.S.R.D. support would be necessary either for Dr. Eagle or Dr. Kolmer.

III. There was next discussed the new technique for titration of traces of reagin described by Dr. Lund (*Am. J. Syph., Gonorr. & Ven. Dis.* 26: 1, 1942). It was the consensus that Dr. Lund's technique offered a valuable method of approach to the quantitative determination of reagin or reagin-like substance in the blood of normal persons and of non-syphilitic persons suffering from other diseases. It was felt that further investigations with this technique were desirable in an effort to determine the following and perhaps additional points:

- A. What proportion of normal persons show this reagin-like factor in their blood in measurable quantities?
- B. Is the reagin-like factor variable in amount at different times in health?
- C. Is this reagin-like factor quantitatively influenceable in normal persons by various procedures, e.g., those calculated to increase antibody content?
- D. Is the reagin-like factor variable during the course of non-syphilitic disease?
- E. What is the quantitative relationship of the reagin-like factor to syphilitic reagin?
- F. What is the quantitative relationship of the reagin-like factor in various normal animal species as compared with man?

It was agreed that Dr. Lund would submit a proposal for contract covering the study of this and related points in his laboratory.

IV. The last three items on the agenda, dealing with the chemical identification of reagin or with the chemical activity of the reacting substance in tissue extract antigens, led to much general discussion but to no conclusion which could be reached by the present Conference. It was sugges-

ted and agreed that, subject to the approval of the Subcommittee on Venereal Diseases, the Committee on Medicine, and the Division of Medical Sciences, National Research Council, there be called another Conference, this time of certain chemists who have been working with the serologists attendant at this Conference on these and related topics, and of a physicist or physical chemist, to be selected by the Chairman of the Subcommittee on Venereal Diseases, of a serologist similarly to be selected, and of the Chairman of the Subcommittee on Venereal Diseases. The chemists in question are: Dr. John W. Wellman, working with Dr. B. S. Kline in Cleveland; Dr. Stacey Howell, working with Dr. John Mahoney in Stapleton; Dr. Herman Brown, working with Dr. Kolmer in Philadelphia; and Dr. Mary Pangborn, working with Dr. Augustus Wadsworth at the New York City Health Department Laboratories in Albany.

\* \* \* \* \*

In summary, the concrete achievements of this Conference are as follows:

(1) That further work should continue with the Kahn verification test, and that the proposal for contract of Dr. Kahn will be further considered by the Subcommittee on Venereal Diseases.

(2) That further work should continue with spirochetal complement fixation tests in the laboratories of Dr. Harry Eagle and John A. Kolmer; and that so far as is now known, financial support from the Office of Scientific Research and Development is not necessary for the prosecution of these studies.

(3) That the Lund technique should be further studied and that Dr. Lund will submit a proposal for contract to the Subcommittee on Venereal Diseases.

(4) That a conference of chemists who have been working in the field of the serology of syphilis be called to determine what, if any, further studies are desirable in the direction of the identification of the chemical nature of reagin or of the reacting substance in tissue extract antigens.

Respectfully Submitted,

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

PLEASE RETURN PROMPTLY TO  
ROOM 328

23 March, 194<sup>2</sup>. <sup>2</sup> Incl <sup>1</sup>

# 4212

Memorandum

CONFERENCE ON CHEMICAL PROPHYLAXIS OF VENEREAL DISEASES

Pursuant to authorization by the Subcommittee on Venereal Diseases at its meeting on March 11, and with the approval of the Committee on Medicine and the Division of Medical Sciences, there was held in Washington on March 23, 1942, a Conference on the chemical prophylaxis of venereal diseases. Present were Dr. J. E. Moore, Chairman of the Subcommittee on Venereal Diseases, and Dr. John F. Mahoney of that Subcommittee; and the following invited guests: Dr. D. M. Pillsbury, University of Pennsylvania, Dr. Harry Engle, (U.S. Public Health Service), Johns Hopkins University, Dr. Louise Pearce, Rockefeller Institute for Medical Research, Princeton, N.J., Dr. H. H. Hazen, Washington, D.C., Chairman of the Committee on Prophylaxis, established under the joint auspices of the U. S. Public Health Service and the American Social Hygiene Association; Lieut. Colonel T. B. Turner, Johns Hopkins School of Hygiene and Public Health, Baltimore, Dr. Charles M. Carpenter, University of Rochester School of Medicine, Dr. W. A. Fleming, University of North Carolina School of Public Health, Chapel Hill, and Dr. Alfred Cohn of the New York City Health Department. Also present were Rear Admiral H. W. Smith and Captain Stephenson, U. S. Navy, Lieut. Colonel Prentiss and Major Gordon, U. S. Army, Dr. Powers of the American Pharmaceutical Association, Doctors Weed and Larkey, Division of Medical Sciences, National Research Council, and Dr. Walker, Committee on Medical Research.

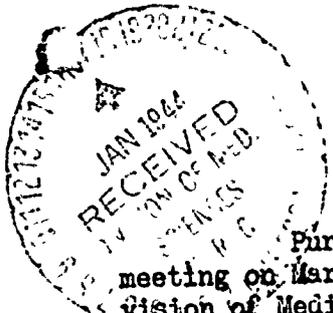
The discussion was opened on the basis of the memorandum of February 14, 1942, on the subject of chemical prophylaxis which has already been appended as Exhibit C to the Minutes of the Fourteenth Meeting of the Subcommittee on Venereal Diseases. The discussion was confined largely on the chemical prophylaxis of syphilis and gonorrhea since the Chairman of the Subcommittee on Venereal Diseases had been authorized to approach personally certain other physicians concerning possible studies in the prophylaxis of lymphogranuloma venereum, chancroid, and granuloma inguinale.

Dr. Mahoney opened the discussion by reporting informally on the unpublished results of some 13 years of study of chemical prophylaxis in his laboratory. He discussed the experimental methods of inoculation of animals and pointed out that that method was desirable which most closely simulated the method of inoculation in human beings exposed by sexual intercourse, i.e., the simple contact of an emulsion of *T. pallidum* with an unbroken mucous surface.

Utilizing calomel ointment, Dr. Mahoney has demonstrated that this substance is effective in the chemical prophylaxis of syphilis when applied as ointment either locally at the point of inoculation or at a distant point on the uninoculated skin. The dose of calomel ointment employed by him in these experiments was 4 grams of the 33-1/3 per cent ointment (1.3 gm. of calomel, an approximate dose of 650 mg. per kilo of body weight, assuming the complete absorption of the calomel).

On the basis of these experiments Dr. Mahoney believes that the action of calomel is largely systemic.

He points out that the penetration of organisms through an unbroken mucous



surface takes place within  $2\frac{1}{2}$  to 4 hours as measured, first, by the effectiveness of locally applied cleansing agents, and, second, by the actual demonstration of stained *T. pallida* in the depths of the tissues; and that any substance, calomel or otherwise, applied to the skin 4 hours or later after exposure can only act in systemic fashion in the early treatment of an already established infection.

Dr. Mahoney adds that in addition to the experiments on soap and water, locally applied antiseptics, such as alcohol, ether, and tincture of iodine, and calomel, which were published in the *Military Surgeon*, 78: 351, 1936, he has likewise experimented with almost a hundred other substances in an effort to prevent the penetration of *T. pallida* into the intact mucous membrane. Among these are various arsenicals, bismuth compounds, mercurial compounds, and sulfonamides in various bases including ointments, glycerin, and wetting agents. The results, however, are essentially negative and he has found no reason to believe that any substance tested by him, except soap and water applied within an hour and a half, or calomel ointment over longer periods of time, is effective.

Dr. Mahoney's statement led to a general discussion of the desirable features of a chemical prophylactic agent against the venereal diseases. It was pointed out that such a preparation should be easily transportable, equally effective against all the venereal diseases, cheap, free from irritating and toxic manifestations, and readily utilizable by the exposed person without the use of auxiliary apparatus. It was suggested that soap and water might be the ideal prophylactic agent for these purposes and that, while experimental proof of it was lacking, the experience in human beings could not be relied upon, and that it was further pointed out that soap and water was not an ideal prophylactic agent because in many cases it could not be utilized at the time and place of exposure.

In connection with the Coast Guard experience, however, a statement by Dr. Carl Michel, Medical Director of the Coast Guard, was read in which Dr. Michel described briefly certain unpublished experiments in animals as to the value of mercuric iodide soap. The Chairman has written to Dr. Michel for detailed information concerning these experiments.

Dr. Mahoney's statement led to a further discussion of the use of calomel ointment. It was pointed out that in all of the experimental work performed by himself, by Metchnikoff and Roux, and by Nichols and Walker, the dose of calomel ointment was either not stated, or this substance was used in a dose far larger than that commonly applied in human beings. For example, in Mahoney's experiments the dose of calomel ointment was approximately 650 mg. per kilo of body weight; as compared with an approximate dose of 18 mg. per kilo of body weight used in human beings. The dose employed by Nichols and Walker was approximately 325 mg. per kilo of body weight, or larger. Making due allowance for the incomplete absorption of calomel ointment in rabbits and for varying degrees of absorption, both in experimental animals and human beings, these discrepancies in dosage raised several questions as to the use of calomel ointment in man. It appears that in the dosage applied in man there is no clear cut evidence that calomel ointment is of any value in the prevention of syphilis, or, if it has any value, whether this value is local or systemic in action.

It seemed desirable, therefore, to the Conference to arrange for further experiments on the value of calomel ointment in the prophylaxis of experimental syphilis. Certain of the invited guests who had available laboratory facilities for this problem met subsequent to the Conference and it was agreed.

That certain experiments looking toward the elucidation of the value of calomel ointment in the prophylaxis of syphilis in experimental animals would be undertaken immediately in the respective laboratories of Doctors A. H. Chesney, Harry Eagle, and T. B. Turner, all of the Johns Hopkins School of Medicine or School of Hygiene and Public Health, respectively. It was further agreed by these investigators that the preliminary experiments could be carried out within a period of 3-4 months without the necessity of applying for additional funds to the Office of Scientific Research and Development, through the Committee on Medical Research.

It seemed probable to the Conference that if these planned experiments indicated that calomel ointment in the dosage currently applied in man had no demonstrable local or systemic effect, it would then be feasible for the Subcommittee on Venereal Diseases to recommend to the U. S. Army and Navy that calomel ointment be dropped from the present prophylactic system as unnecessary, unpleasant, and of no value. On the other hand, it seemed probable to the Conference that if those preliminary experiments demonstrated that calomel ointment did have any effect, whether local or systemic, it would then be desirable to elaborate further investigations looking toward the use of this substance in a more efficient base than in the greasy ointment bases now available. Should such further experiments prove to be desirable, it was the feeling of the Conference that it would then probably be necessary to call in the facilities of other laboratories of experimental syphilis, e. g., those of Dr. Louise Pearce at the Rockefeller Institute for Medical Research, Dr. W. A. Fleming, University of North Carolina, and possibly of Dr. Charles M. Carpenter at the University of Rochester.

In the meanwhile it was agreed that Dr. Mahoney would continue in his own venereal disease research laboratories at Stapleton, S.I., further studies of substances other than calomel.

It was pointed out by representatives of the Army and Navy present that in this particular experimentation time is of the essence and that an early answer is desired, if it can be obtained, as to (a) the suitability of calomel ointment in prophylaxis; or (b) the availability of some more potent substance.

There then ensued a general discussion of emulsion bases, wetting agents, and other substances which may enhance the penetrability of drugs into the skin. Since those represented at the Conference had relatively little readily available information on this point, it was agreed that Dr. D. M. Pillsbury should summarize current knowledge as to these substances (including if possible the new skin penetrant for which Drs. Marion Sulzberger and David Barr already have an O.S.R.D. grant in connection with the study of vesicant gases); and that Dr. Pillsbury

would include with his summary suggestions as to what, if any, further investigations are desirable along these lines; and, if any, who and where are investigators qualified to carry them out.

It was further agreed that additional experiments were desirable to determine the effectiveness of soap in the prophylaxis of syphilis; to determine the time limits of survival of treponemes at various pH, and to determine whether the treponemocidal action of soap is dependent on pH or on some other intrinsic factor. It was agreed that preliminary experiments in this direction should be carried out in the laboratory of Dr. Harry Ligie.

As to the chemical prophylaxis of gonorrhoea, the discussion was less profitable. It was generally agreed that, in order to determine the effectiveness of prophylactic agents, only three methods of approach seemed feasible. These are:

(a) In vitro studies of the effectiveness of various antiseptic agents. As to this the Conference was of the opinion that in vitro studies were not readily translatable to human beings.

(b) The production of gonococcal infection in the genital mucosa or conjunctiva of experimental animals. The attitude of the Conference on this point was relatively hopeless since a number of such experiments have been done with entirely negative results. On subsequent consideration of this topic by the Chairman of the Subcommittee on Venereal Diseases and by Dr. Arthur H. Walker of the Committee on Medical Research, however, it appears that excepting the experimental work of Dr. Phillip Miller, little or nothing has been done in the attempt to produce experimental gonorrhoea during the past 10 years, and a number of possible avenues of approach suggest themselves. Both Dr. Walker and Dr. Moore, subsequent to the Conference, have approached various potentially interested investigators and at least one of these, Dr. Justina Hill of the Brady Urological Institute, Johns Hopkins Hospital, has signified her willingness to attack the problem from various new angles and in the near future will probably submit a proposal for contract to the Office of Scientific Research and Development through the Committee on Medical Research. If it proves feasible to produce gonorrhoeal infection in experimental animals, there would be provided a ready approach to the effectiveness of chemical prophylactic agents.

(c) The production of experimental gonorrhoea in human volunteers with the trial of chemical prophylactic agents in them. After considerable discussion concerning the difficulty of obtaining human volunteers, it was suggested that the Chairman write to Captain Stephenson, U. S. Navy, and to Lieut. Colonel Turner, U.S. Army, enquiring as to the feasibility of conducting such human experimentation on a volunteer basis in the Army and/or Navy. An identical letter was written to Captain Stephenson and Lieut. Colonel Turner (the Army copy of) which is herewith appended as Exhibit A. To this letter a reply has already been received from Lieut. Colonel Turner from which is quoted in part, as follows:-

"I personally believe that it would not be desirable at this time to use soldiers for studies of this nature, and I am not prepared to support such a proposal."

It was pointed out by Captain Stephenson that certain similar studies on human volunteers had been carried out by Dr. R. J. Bachman, U.S. Navy Medical Corps, Retired, and it was suggested that the Chairman write to Dr. Bachman for further information.

The remainder of the discussion concerning gonorrhea centered around the possibility of demonstrating by various statistical methods the value of prophylactic agents currently in use or thought to be desirable for trial. Among these were the following suggestions:

(a) Dr. Alfred Cohn suggests the local treatment of very early cases of acute anterior urethritis with sulfathiazole in various ointment emulsions or wetting agent base. With this suggestion a member of the Subcommittee on Venereal Diseases comments: "The suggestion is based on the fallacy that something of an antiseptic nature can be instilled into the urethra and destroy the cocci that are in the submucous spaces far beyond its reach...We cannot detect early acute anterior urethritis until there has been penetration of the mucosa by the organisms." He believes that Dr. Cohn's proposal is probably without value.

(b) A suggestion by Dr. Charles Carpenter that a human experiment be carried out in the colored caddies of the Sea Island Golf Club, Brunswick, Georgia. The consensus of the Conference was that this experiment would be relatively uncontrolled.

(c) The suggestion was made that in various Army and Navy areas the use of silver proteinate solutions be abandoned and that other substances be substituted, the results to be measured on a statistical basis. The consensus was that information of this sort would be difficult to obtain and still more difficult to interpret.

In summary, the concrete achievements of this Conference are as follows:-

- 1) That certain experiments regarding the prophylactic activity of soap will be undertaken in the laboratory of Dr. Harry Eagle.
- 2) That certain experiments as to the prophylactic activity of calomel ointment will be undertaken in the laboratories of Doctors A. M. Chesney, Harry Eagle, and T. B. Turner.
- 3) That certain experiments looking toward the production of gonococcal infection in experimental animals will be undertaken in the laboratory of Dr. Justina Hill and perhaps of other workers.
- 4) That Dr. Donald M. Pillsbury will summarize for the benefit of the Subcommittee on Venereal Diseases existing knowledge as to skin penetrants. (Dr. Pillsbury's report is herewith appended as Exhibit B.)

For the time being the financial support of the Office of Scientific

Research and Development is not necessary for the first, second, and fourth of these projects. A proposal for contracts will probably be made in the near future by Dr. Justina Hill of the Johns Hopkins University in support of an experimental effort to produce gonococcal infection in animals.

Respectfully submitted,

J. E. Moore, M.D., Chairman,  
Subcommittee on Venereal Diseases  
National Research Council.

March 23, 1942.

T. 1.

EXHIBIT A

To Memorandum of Conference on Chemical Prophylaxis  
of Venereal Diseases

804 Medical Arts Building  
Baltimore, Maryland.

March 24, 1942.

Lieutenant Colonel Thomas E. Turner (MC)  
Division of Preventive Medicine  
Office of the Surgeon General U. S. Army  
War Department  
Washington, D.C.

Dear Colonel Turner:

The Subcommittee on Venereal Diseases is interested in the possibility of improving methods of chemical or chemotherapeutic prophylaxis for gonorrhea.

It is unnecessary to draw to your attention the fact that at present, as for the past quarter century, gonorrhea usually ranks first, sometimes second, as a cause of loss of man days in the U. S. Army; and that any procedure which would reduce the incidence of this disease would be highly desirable from the military standpoint.

The known facts as to the chemical prophylaxis of gonorrhea are relatively meager. It is known that the use of silver proteinate compound in solution, as given at prophylactic stations, is of some value in the prevention of this disease, though it is not definitely known whether these substances certainly protect, nor is there available adequate information as to the time limits of their effectiveness following exposure.

There is literally no information as to the prophylactic value of other substances and particularly of those recommended for personal (kit) prophylaxis. Certain of these, e.g., silver picrate, oxyquinoline sulphate, etc., have been selected by manufacturers on theoretical grounds; and in spite of the lack of evidence of their value, are in current use in Army or Navy.

The Subcommittee on Venereal Diseases has discussed, with the aid of qualified investigators in the field, various methods of approach to determine the efficacy of chemical substances recommended for personal prophylaxis, including in addition to those named above, the local or systemic use of the sulphonamides. It is agreed that in vitro studies of the gonococidal properties of various substances are of relatively small value. In view of the insusceptibility of all known animal species to gonococcal infection, either in the urethra or conjunctiva, experimental studies of the value of such substances in animals is impossible.

The Subcommittee on Venereal Diseases believes that the only satisfactory avenue of scientific approach to the elucidation of this problem is the use of human volunteers, in whom it would be possible to set up a controlled study of the

Lieut. Col. Turner -2

3/24/42

value of chemical substances proposed for the prophylaxis of gonorrhoea.

The Subcommittee believes that such a study in human volunteers is of the utmost importance, in view of the probable increased desirability of personal, as opposed to station, prophylaxis in the armed forces during the present war.

May I therefore enquire as to the feasibility of setting up a human experiment, using as subjects volunteers from the U. S. Army? It is suggested that a precedent for such human experimentation on volunteers from the armed forces already exists in the cases of yellow fever and dengue. It is pointed out further that at the time of the human experiments on yellow fever, this disease carried a high mortality rate and there was no known specific treatment for it. It is pointed out further that in the case of dengue, and although the mortality rate was insignificant, the disease was uncomfortably incapacitating. Still further, neither yellow fever (except in the case of epidemics) nor dengue were diseases of such importance to the manpower of the armed forces as gonorrhoea.

In contrast to the relative gravity of human experimentation in the two diseases named above, it is pointed out that the modern chemotherapy of gonorrhoea renders this disease readily treatable, curable within a short period of time in a very high proportion of cases, and practically without serious complications.

In the opinion of the Subcommittee, the importance of gonorrhoea to the armed forces and its ready manageability in those human volunteers who might become infected, either while serving as controls or as a result of failure of the chemical prophylactic substances employed, is complete justification of the suggestion that such an experiment be set up with the cooperation of the U. S. Army.

Would you be good enough to present this point of view to the proper military authority and to let me know whether in your opinion it would be possible to arrange such a human experiment on a volunteer basis?

Sincerely yours,

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

JEM:G

EXHIBIT B

Memorandum on Emulsion Type Ointments, and Skin Penetration  
in Relation to Prophylaxis against Genito-Infectious Disease

In this memorandum it is proposed to set up criteria for a vehicle for prophylactic ointments and to indicate to what extent the available data regarding emulsions and skin penetrants allow of a solution of this problem.

Attributes of "Ideal" Vehicle

1. Facilitate an adequate concentration of the selected spirocheti-  
cidal, bactericidal, and anti-virus drug or drugs (a) under  
crusts, smegma, and scales, and/or (b) in the lower layers of  
the epiderm and papillary layer of the cutis.
2. Permit maintenance of adequate concentrations of chemicals on  
and within the skin, and not act simply as a means of facili-  
tating the passage of chemicals through the skin into the  
circulation.
3. Be miscible with water and serum, and facilitate mechanical  
cleansing of the skin.
4. Be non-irritating, non-staining, and stable.
5. Be composed of cheap and easily obtainable materials.
6. Not facilitate the entrance of live spirillar or coccal organ-  
isms or virus materials through the skin and mucous membrane.
7. Be capable of urethral injection as well as local application  
to the skin.
8. Permit of desired variations in pH.

The available knowledge bearing on this problem may be considered from four standpoints: (1) the emulsion type ointments, in which a mixture of oil and water is obtained by the use of suitable concentrations of emulsifiers and wetting agents, and concerning which there is some experimental and clinical experience; (2) the physiology of penetration of the skin by various substances, which can be summarized only in part here, with some indication of the gaps in the available knowledge; (3) certain newer skin penetrants, which as yet have had little clinical application; (4) the relative efficiency of spirocheticidal, antibacterial, and anti-virus chemicals on local application to the skin and mucous membranes.

Emulsion Type Ointments. The development and use of emulsifying and wetting agents in recent years has made available various new types of ointment bases which are water soluble, easily applicable to hairy surfaces and miscible with serous and purulent exudates. (Mumford, P.S., Brit. Jour. Dermat. and Syph. 50: 540, 1938.

Duemling, W. W., Arch. Dermat. and Syph. 43: 264, 1941). In addition, laboratory studies in vitro have indicated that emulsion bases, particularly the oil-in-water type, increase the effectiveness of incorporated bactericidal agents as compared to standard all-grease bases such as petrolatum and simple ointment (Gershenfeld, L., and Brillhart, R.E., The Amer. Jour. Pharm. 111: 430, 1939). Such laboratory studies may not, however, be an accurate indication of the clinical effectiveness of such agents on the skin (Livingood, C. S., Pillsbury, D. M., Nichols, A. C., The Bactericidal Effects of Antiseptics Incorporated in Ointment Bases of Various Types, in press).

An emulsion may be defined as a homogeneous stable suspension of small drops of one liquid in another with which the former is normally not miscible. Emulsion ointments may be solid or semi-solid, and may contain 70 per cent or more of water. When the oil or wax is dispersed in the form of tiny drops in the water, the resulting emulsion is said to be the oil-in-water type (water soluble) which may be diluted with water, and when the water is dispersed in the oil or wax, the emulsion is the water-in-oil type which may be diluted by the addition of oil. The number of emulsifying agents now available is large, and they will only be listed here: esters of glycerine and glycols, triethanolamine and its salts, complicated amines and their soaps, and lecithin. Detailed discussions are available in the following sources: de Navarre, H.G. Emulsions. Bull #7, The American Perfumer, September 1938; Clayton, W. Theory of Emulsions, P. Blakiston, Philadelphia; Alexander, J., Colloid Chemistry, D. van Nostrand, New York; and others.

As a vehicle for the application of prophylactic chemicals, emulsion ointments would probably have the following advantages and disadvantages:

#### Advantages

1. Promote intimate contact of the incorporated chemical with the surface of the skin or mucous membrane. This has been demonstrated with reasonable certainty in the local application of sulfonamides (Pillsbury, D.M., Livingood, C.S., and Nichols, A.C., Am. J. Med. Sci. 202: 808, 1941).
2. May be prepared in various consistencies and are stable.
3. Assist in cleansing of the skin, and may be substituted for soap.
4. Are relatively cheap, though more expensive than some all-grease ointments.
5. May be applied easily to hairy areas, are easily removed, and do not stain.
6. Do not require long-continued inunction.
7. May be adjusted to a wide range of pH.

### Disadvantages

1. Probably do not promote penetration of a contained chemical through the stratum corneum and epidermis in a short time; i.e., 2-3 hours. While the limited studies of Pueling, indicate that penetration of fat along the hair follicles to a depth just below the basal layer of the epiderm may be obtained in 15 minutes following the application of an ointment containing a wetting agent, there is no indication that this would occur through intact non-hairy skin, nor that all chemicals incorporated in such a base would be carried along with the fat. Pueling has demonstrated by a non-quantitative staining technique that ammoniated mercury is carried to the deeper layers of the epiderm, but our clinical experience has given no indication that such ointments have a bactericidal effect in the deeper portions of the skin. In addition, there is no indication that a substance such as sulfathiazole may be introduced into the circulation in significant amounts by application to the intact skin in emulsion vehicles.

It is emphasized that because an emulsion vehicle may be demonstrated in the deeper layers of the skin shortly after application, it cannot be assumed a priori that all contained chemicals would be carried along with the vehicle nor that such chemicals would necessarily be active within the tissue.

2. Emulsion type ointments occasionally produce contact dermatitis, though probably in less than 0.1 per cent of patients.

Penetration of Skin. The data regarding penetration of the intact skin and mucous membrane by various substances will be summarized only briefly. There is abundant evidence that this occurs with a variety of applied substances, e.g., hormones, vitamins, salicylic acid, sulphur, metallic mercury, thallium acetate, animal fats. The factors which facilitate or inhibit penetration are not clearly understood, and experimental results in animals are often not applicable to man because of differences in structure of the skin (such as the absence of sweat glands) and unknown factors. In planning an experimental attack on this problem, the following general methods may be considered:

1. The passage of substances through the skin into the blood stream as determined by:-
  - a. Excretion in the urine, e.g., salicylic acid, (Moncorps, C., Arch. f. Exp. Path. u. Pharmacol. 141: 1, 1929.)
  - b. Blood concentration, e.g., sulfonamides (Pillsbury et al. loc. cit.)
  - c. The physiologic effects of incorporated substances, e.g., strychnine and insulin (Starkenstein, E., and Mandrych, Arch. f. Exp. Path. u. Pharmacol. 182: 664, 1936).

The above cited methods have the advantage of some applicability to the study of the penetration of human skin. On the other hand, they are indicative only of penetration through the skin, and in general give no information concerning the level of the contained chemical within the skin itself. It must also be kept in mind that substances which may facilitate the penetration of one compound through the skin may not act similarly with another compound. This has been well shown, for instance, with sulphur and with salicylic acid (Moncorps).

2. The level of an applied substance within the skin as demonstrated by special stains, and darkfield examination:-
  - a. Special fat stains, (Duenling, loc. cit., Eller, J.J., and Wolff, S.: Arch. Dermat. and Syph. 40: 909 1939).
  - b. Darkfield demonstration of metals, e.g., silver (Hill, W.R., and Pillsbury, P.M., Argoria, Williams and Wilkins, 1940).
  - c. Spectroscopic or chemical determination of skin after application of metals. I know of no reports using such methods, though they probably exist.
  - d. Special counterstains for applied substances in vivo, e.g., demonstration of sulphur by combing with injected bismuth (Moncorps, loc. cit.).

These methods have, I believe, certain disadvantages as a means of predicting the spirocheticidal or bactericidal effects of a particular chemical compound in man. They are usable with difficulty in a study of the human skin because of the necessity of obtaining biopsy material. Experiments on animal skin may not indicate similar penetration into human skin. The substance carried into the skin may or may not have an effect similar to that noted in vitro or on the skin surface. The staining methods are not quantitative. The spectroscopic and chemical methods give no indication of the amount of chemical on the surface of skin or in its deeper layers, respectively.

Newer Types of Penetrant Vehicles. In answer to an inquiry, Dr. Marion B. Sulzberger writes as follows:-

"The principles involved in the vehicles are the following: They are mixtures of wetting agents, such as Aerosol MA and Aerosol 1B of the American Cyanamid Company, or paraxylene sulfonate plus propylene-glycol and pyrazolon derivatives such as antipyrine. I will not go into the theoretical reasons for these mixtures, but simply state now that our preliminary trials indicate that the three principal types we have developed serve different purposes; two being more suitable for dissolving oily and fatty substances and for penetrating into oils and fats, and one being more suitable in an aqueous medium. Our trials thus far demonstrate that a variety of substances are carried through the grossly intact skin at a much greater rate than was heretofore possible. The substances which

have been included in our first trials are bismuth, iron, numerous and varied allergens, adrenalin, and with less certain effects, insulin and sulfonamides. Another property of these vehicles is that they take up in neutral solution (or apparent solution) chemicals which are often relatively insoluble, such as the sulfonamides.... The U. S. Government and its agencies are to have free use and access to these materials and their future developments."

Dr. Julzberger has supplied the formulae for the various penetrating vehicles, and has offered his cooperation in their possible use in a prophylactic ointment.

These vehicles would seem to have great potentialities for the introduction of prophylactic chemicals through the skin. It is conceivable, however, that they might also permit more rapid penetration of the skin and mucous membrane of the urethra by micro-organisms and viruses. Before they are applied clinically, this point requires study.

Relative Efficiency of Spirocheticidal, Antibacterial, and Antivirus Drugs.

The writer is not qualified to make more than a few general comments on this important phase of prophylaxis. It might be pertinent to point out that studies of mercurial antiseptics done in our laboratory have shown them to be relatively ineffective against staphylococci and streptococci on the skin, and that in vitro studies are often only an indication of the rate of diffusion of a mercurial substance through an agar medium, and are untrustworthy indicators of clinical effectiveness. Mercurial antiseptics have acquired a tradition of effectiveness by many years of use, and this writer, at least, doubts that this tradition is justified. Calomel is, on the whole, such a relatively weak antiseptic and antisyphilitic drug that a searching investigation of its actual performance as a spirocheticidal prophylactic substance seems justified.

Sulfathiazole incorporated in an emulsion type vehicle is so effective against surface skin pyococci, that its trial as an antigonococcal agent when applied locally to the urethral mucous membrane seems indicated. With newer methods it would seem that the relative clinical effectiveness of various sulfonamides against gonococci may be predicted with some accuracy by invitro studies.

If a stable arsonoxide compound could be developed for incorporation in a prophylactic ointment, it seems probable that it would be much more effective than an antisyphilitic drug as ineffective as calomel.

On the basis of an extended summary with Hill (loc. cit.) the writer doubts that the popularity of silver compounds as local antiseptics is entirely justified. Certainly they should be re-evaluated in comparison with the sulfonamides as regards local anti-gonococcal action.

The following recommendations are submitted:

1. That an attempt be made to develop a stable semi-fluid oil-in-water emulsion type ointment easily applicable to the genitalia, and injectable into the urethra. With the desired sulfonamide incorporated, such a preparation could be sent out for immediate clinical trial in the treatment of gonorrhea, as suggested at the recent Conference. Its practicability and freedom from irritative effects could be determined quickly. The following formula might be suitable:

*Sulfathiazole	5.0%
Sodium lauryl sulfate	1.0%
Stearyl alcohol	10.0%
Cetyl alcohol	3.0%
Spermaceti	10.0%
Glycerine	10.0%
Water	61.0%

\* Particles not over 10 micra in size

2. In collaboration with Dr. Marion E. Sulzberger, determine the effect of his newer vehicles in increasing the penetration of spirochetes through the skin of animals; whether or not this could be prevented by the incorporation of spirocheticides.  
Suggested investigators: Harry Eagle, T. B. Turner, John Mahoney.
3. Determine the effectiveness of calomel, sobisminol mass, arsenoxide and other possible spirocheticides incorporated in emulsion type and newer penetrant vehicles on eroded and uneroded mucous membrane and skin lesions of early syphilis in man. Under conditions of suitable control, such experiments would not seem to involve unjustified danger to the patient or to the public health.  
Suggested investigators: J. E. Moore, John H. Stokes, D. M. Pillsbury, M. E. Sulzberger.
4. Set up an advisory group on the pharmaceutical aspects of a prophylactic ointment. Chemists in various pharmaceutical phases are probably best qualified. The following problems present themselves:
  - a. Is it possible to develop a stable arsenoxide compound for local use?
  - b. If it is found advisable to retain a mercurial in a prophylactic ointment, what is the best compound?
  - c. Is a more finely divided colloidal form advisable? (This might result in more effective action and saving of chemicals, e.g., colloidal calomel, micro-sulfonamides, etc.)
  - d. What are the possible incompatibilities, e.g., silver and arsenoxide, sulfonamide and mercury? Standard tests of extremes of temperature, "shelf" test, etc., would be required. The following manufacturers have had considerable experience:

- (1) Emulsion bases - Smith, Kline and French Laboratories
- (2) Newer penetrants - Lederle Laboratories.
- (3) Arsenoxide - Parke-Davis, Squibb, Abbott.
- (4) Silver compounds - Squibb, Lilly, John Wyeth.
- (5) Sulfonamides - Lederle, Abbott, Squibb, Smith, Kline and French (micro-sulfonamides).

It is felt that projects to study the penetration of various substances through the skin of animals and man might require considerable time before results of practical importance would be achieved because (a) there would be some delay in starting such projects; (b) results in animals would require clinical confirmation. However, the following persons are suggested as worthy of consideration if such projects are desired:

Physiology of Penetration of Skin

1. Dr. Hamilton Montgomery, Mayo Clinic, Rochester, Minnesota.
2. Dr. K. K. Jones, Department of Physiology, Northwestern University, Chicago, Illinois.
3. Dr. S. W. Becker, Department of Medicine, University of Chicago.

Clinical and Laboratory Aspects of Emulsions, Wetting Agents, and Newer Penetrants.

1. Dr. Marion B. Sulzberger, 962 Park Avenue, New York.
2. Dr. Bertram Shaffer, Department of Dermatology and Syphilology, University of Pennsylvania, Philadelphia, Pa.

Respectfully submitted,

Donald M. Pillsbury, M.D.

RECORD

NATIONAL RESEARCH COUNCIL

DIVISION OF MEDICAL SCIENCES

Minutes of the Conference between Members of  
the Subcommittee on Neurology and the Subcommittee on Venereal Diseases  
on the subject of Neurosyphilis

March 11, 1941

On Tuesday, March 11, 1941, a conference on the subject of Neurosyphilis was held between members of the Subcommittee on Neurology and the Subcommittee on Venereal Diseases. Those present were: Drs. Perry Pepper, presiding, Lewis H. Weed, Winfred Overholser, J. E. Moore, J. F. Mahoney, John H. Stokes, Foster Kennedy, Harry C. Solomon, Sanford V. Larkey, E. H. Cushing, Capt. Charles S. Stephenson, Capt. Dallas Sutton, Lt. George W. Mast, Lt. Col. James C. Kimbrough, and Capt. James H. Gordon.

Dr. Weed, in opening the meeting, stated that there had been differing points of view in the recommendations from these two committees, and it was felt that a conference might resolve these differences. He asked Dr. Pepper to preside.

Dr. Overholser said that in making its recommendations, the Subcommittee on Neurology felt that neurosyphilis was different from the other organic manifestations of syphilis, and that, because of these manifestations, the Subcommittee felt that the treatment should be under the direction of neuropsychiatrists.

Dr. Pepper then called on Col. Kimbrough to tell of the present arrangements in the Army. Col. Kimbrough said that generally all cases of syphilis were kept in the venereal disease ward until such a time as neurological symptoms developed, at which time there was a consultation with the neurologist for advice as to the type of treatment to be used in the case. Even when the patient was on the neuropsychiatric ward, the actual technique

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of treatment was given by the venereal disease specialist. The venereal disease section is a section of surgery.

Capt. Sutton then told of the arrangements in the Navy, where neuropsychiatry and neurosyphilis are in the division of medicine. Symptomatic cases of neuropsychiatric syphilis are not sent to the venereal disease section. Malaria treatment and head treatment are under the direction of the neuropsychiatric service. Capt. Stephenson amplified this statement saying that in at least one hospital that he knew of, all the syphilis was cared for on the genito-urinary service, a section of surgery.

Dr. Moore told of the background of the recommendations of the Subcommittee on Venereal Diseases and read the recommendation from the meeting on January 17. ( See below.) He said that it was the opinion of the committee that the present method of the Army of placing venereal diseases under the genito-urinary service should be abandoned. The committee had recommended that a section on venereal disease control should be established and that all venereal diseases and particularly syphilis should be treated by men with special training in venereal diseases. Dr. Stokes agreed with the statement of Dr. Moore.

Dr. Kennedy then read the recommendation of the Subcommittee on Neurology:

"Resolved: that, in the case of any individual discharged from the service who had contracted cerebrospinal syphilis or who at any time during his service was found to be suffering from cerebrospinal syphilis, information of such discharge and the identity of the individual discharged shall be transmitted to some Public Health or other agency operating in the vicinity of the home of the individual, in order that further supervision and observation over such an individual could be exercised for as long a time as was deemed necessary."

"Be It Resolved: that it is the sense of the Subcommittee on Neurology of the Committee on Neuropsychiatry that neuropsychiatric disabilities and disorders when caused

by syphilis should remain, as is the present practice, in the hands of neuropsychiatrists for treatment and observation."

It was pointed out that the first resolution was consistent with similar recommendations from the Subcommittee on Venereal Diseases.

Dr. Kennedy then asked Dr. Solomon to state the position of the Subcommittee on Neurology. Since long training is necessary for the proper handling of the neuropsychiatric manifestations of syphilis and the prevention of later symptoms, it was the opinion of the committee that neuropsychiatrists should, from the first recognition of involvement of the central nervous system, be in charge of the case. He did not feel that all syphilologists were competent to handle the neurological aspects.

There was considerable discussion along these lines, each group admitting that some members of the opposite group would be competent. Dr. Stokes proposed that conference rather than individualistic specialization be the basis of the later manifestations of syphilis.

It was decided that the recommendation of the Subcommittee on Venereal Diseases would be satisfactory to all, with the addition of a sentence suggested by Dr. Moore. This recommendation would then read:

"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. The diagnosis, treatment and general management of the many late manifestations of syphilis should naturally require conference and consultation between the several medical specialties involved, with transfer of responsibility as necessary for administrative or medical reasons to special services (such as medical, neuropsychiatric, ophthalmologic, etc., etc.)"

It was moved by Dr. Kennedy and seconded by Dr. Solomon that the conference approve this amended recommendation. Unanimously approved

The memorandum on the treatment of neurosyphilis, prepared by Dr. Solomon, was then discussed. It was felt that it was not quite adequate for the purpose of a service manual, and Dr. Solomon was asked to revise this, with more emphasis on the handling of emergencies in neurosyphilis.

It was moved by Dr. Larkey and seconded by Dr. Overholser that the joint recommendations of this committee be sent to the Committee on Neuropsychiatry for action and forwarding.

The meeting adjourned at 12:15 p.m.

# END

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