To J. B. Donovan
To be returned to A. N. Richards

CABLE ADDRESS: NARECO
WASHINGTON, D. C.

NATIONAL RESEARCH COUNCIL

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CONFIDENTIAL

Dr. A. N. Richards, Chairman
Committee on Medical Research
National Research Council
Washington, D.C.

Dear Doctor Richards:

This letter is in support of the desirability of carrying out experiments in the chemical and chemotherapeutic prophylaxis of gonorrhea in human volunteers selected from prison populations, as exemplified by the proposals for OSRD contract of Carpenter, University of Rochester (for work in Georgia, North Carolina, or New York), of Miller, University of Chicago (for work in Illinois), of Cohn, New York City Health Department (for work in New York), and possibly of others which may subsequently be submitted.

I. The importance of the problem to the Armed Forces:- The current incidence of fresh infections with gonorrhea in U.S. Army and Navy is roughly 35 per 1000 strength per annum. The publicly announced strength of Army and Navy (including Marines and Coast Guard) for 1943 is in excess of 10,000,000 officers and men. If the present incidence of gonorrhea cannot be materially reduced, and if indeed it does not rise (which may be anticipated with military personnel serving abroad), there will be, during 1943 (and during each subsequent year in which incidence rate and strength of personnel remain the same), approximately 350,000 fresh infections with gonorrhea. Assuming an average loss of time of 20 days per infected man (the actual figure for Army in recent years to 1941 was 35 - 45 days, for Navy 10 - 15 days), this will account for 7,000,000 lost man days per year, the equivalent of putting out of action for a full year the entire strength of two full armored divisions or of ten aircraft carriers.

II. The prophylactic systems now in use in U.S. Army and Navy and their effectiveness:- Three methods are in common use in Army and Navy for the prophylaxis of the venereal diseases, and a fourth has undergone some tentative trial. These are:-

a) Mechanical, through the wide distribution of condoms. If properly used, these appliances are effective against gonorrhea; but against the other venereal diseases (syphilis, chancroid, lymphogranuloma venereum, and granuloma inguinale) condoms protect only the part actually covered.

However, condoms are less widely and properly used than they should be, because of disinclination, unavailability at the moment, ignorance, or carelessness. Reliance cannot be placed on them alone.

b) Chemical prophylaxis, administered by attendants at prophylactic stations to which men are directed to report after sexual exposure. Here the procedure consists of several steps which, together with their supposed action, are as follows:-

1. Preliminary urination (designed to wash pathogenic organisms out of the urethra).
2. Washing the genitalia with soap and water (supposed to protect, at least in part, against all the venereal diseases except gonorrhea).
3. The intraurethral injection of a silver proteinate solution (against gonorrhea).
4. Local application of 33% calomel ointment (against syphilis).

IV (d)(1)

The efficacy of station prophylaxis, applied as above, and if prophylaxis is taken within a brief time after exposure (preferably within one hour), has been demonstrated for gonorrhea and syphilis (though not for the three minor venereal diseases) by long Army and Navy experience. The demonstration of efficacy has been relative rather than absolute (see paragraph IV d1 below); but it is clear that station prophylaxis does accomplish some good.

However, station prophylaxis is open to serious objections, more so in this war than in the last. It is embarrassing, revelatory to fellow soldiers and sailors, mildly uncomfortable, time-consuming, and messy. It is difficult to persuade exposed personnel to report for such prophylaxis soon enough after exposure. In this war, the mechanization of personnel and of prostitutes as well, makes the time factor even more important, since many exposures occur miles away from the nearest prophylactic station.

c) Chemical prophylaxis, self-administered by the exposed soldier or sailor from a "prophylactic packet", designed to be used immediately after and at the place of exposure. Most of these packets attempt to reproduce the features of station prophylaxis, and provide a soap impregnated cloth (for washing), and one or two collapsible ointment-containing tubes. Some packets provide separate tubes for calomel ointment and for an ointment or jelly containing a silver salt or other supposedly gonococcicidal substances; others incorporate the supposedly gonococcicidal chemical (many different such chemicals have been used, but not as yet a sulfonamide or an arsenical -see below) into the calomel ointment in a single tube.

This system also is of some value in the prevention of syphilis; but there is literally no knowledge as to whether it accomplishes anything against the other venereal diseases, including gonorrhea. Not only are prophylactic packets so far devised of undemonstrated efficacy, but most of them are unnecessarily complicated, equally as messy as station prophylaxis, and far from generally employed by exposed men.

d) Chemotherapeutic prophylaxis by means of the oral administration of sulfonamide drugs. This system has been shown to be efficacious against gonorrhea by certain Army and Navy experience, and against chancroid by certain planned experiments under the auspices of the Subcommittee on Venereal Diseases, National Research Council (see below). It may also be effective against lymphogranuloma; is known not to be effective against syphilis; and there is no knowledge of its efficacy (or that of any other prophylactic system) against granuloma inguinale.

There are two major objections to the oral use of the sulfonamides for prophylactic purposes in the Armed Forces, objections so serious that even without definite facts concerning them, such use of these compounds either already has been or is about to be forbidden by Army and Navy. These are:- (1) that mental alertness and muscular coordination may be impaired, especially significantly in flying personnel and in e.g. gun-pointers; (2) that sensitization may occur, thus increasing risk in the event of subsequent combat injury. These two objections should be, and are being, more accurately delineated by certain experimental work fostered by the Subcommittee on Venereal Diseases, National Research Council.

III. The cost of present prophylactic systems:- It is reliably reported that the U. S. Army alone will expend in 1943 $34,000,000. for prophylactic supplies, chiefly chemical.

IV. The scientific background of present and future prophylactic systems:- Station or packet chemical prophylaxis, when carefully analysed, is found to be based on much a priori reasoning and very little observed experimental fact. Let us consider the several venereal diseases one by one:-

Syphilis:- Thirty three per cent calomel ointment has been shown to be efficacious against this disease in experimental animals. (Metschnikoff and Roux, Nichols and Walker, Mahoney); but these earlier studies were carried out without regard to dose/weight relationship. Where this was considered at all, doses were used in animals 15 to 30 times in excess of the possible dose in man. Only recently have Eagle and his associates shown (working in collaboration with the Subcommittee on Venereal Diseases, National Research Council) that calomel is effective in preventing rabbit syphilis when used in doses comparable to those used in man. Even now, certain further points relating to calomel (particle size, inhibitory effect, if any, of added chemicals such as sulfonamides, improved vehicles) require much further study.

Meanwhile, preliminary studies by Eagle and Mahoney indicate that an arsenical drug locally applied may be far more effective than calomel.

Chancroid:- It has now been demonstrated by investigators for OSRD (Greenblatt, Combes and Canizares) that no one of the steps of the present Army and Navy prophylactic systems protect against this disease, so

important in the personnel stationed in the tropics. Soap and water and calomel are alike ineffectual. On the other hand, sulfonamides orally or applied locally will protect. The arsenicals are being studied in view of their promising overall activity against syphilis, gonorrhea, and lymphogranuloma.

Lymphogranuloma venereum:- Until recently, nothing whatever was known of the prophylaxis of this disease, also important in the tropics. It has now been demonstrated by Rake, working under OSRD contract, that the arsenicals are the most promising virucidal substances so far tested.

Granuloma inguinale:- Nothing known as yet, though experiments are planned in human volunteers already infected with this disease.

Gonorrhea:- This disease, numerically and in point of lost manpower the most important of the lot, has purposely been left till last, since it forms the major topic of this communication.

The use of silver proteinate in station prophylaxis was begun by Army and Navy because, in the pre-sulfonamide days, the local instillation of these substances into the urethrae of patients already infected with gonorrhea seemed to be of some curative value. It was assumed, probably correctly, that if e.g. protargol will cure the disease, it ought also to prevent it. Since no experiments were carried out, however, except the unsatisfactory one of actual field usage (See paragraph Vd1) nothing definite is known of the time interval after which these drugs fail to protect, nor is it known whether protection is relative or absolute.

The use of silver salts or other compounds in packet prophylaxis rests on an even shakier foundation than this. These substances whose name is legion, have been utilized because they showed some gonococcicidal activity in the test tube, and there is no information as to their efficiency in actual practice.

Summary of present prophylactic systems; their demonstrated value; available methods of study of present and improved systems; the value of such methods of study; work actually in progress; and leads so far furnished by that work: Table I shows that present chemical prophylactic

(Table I follows)

Table I

Summary of Present Prophylactic Systems, showing Method of Study and probability of replacement of present by entirely new and more effective systems.

Disease	Effective agent in present prophylactic systems	Available methods of study of these or other prophylactic agents	Value of such methods of study	Studies in progress under auspices of Sub. on V.D.	Leads available as to improved methods of chemical prophylaxis (listed in order of probable efficiency
Gonorrhea	Silver proteinate solution	In vitro (test tube)	Minimal	+	Sulfonamides locally or orally
		In experimental animals	Unavailable	? See text	Arsenicals
		In human volunteers	Definitive	See text	
Syphilis	Calomel ointment	Experimental syphilis in rabbits	Probably definitive	+	Arsenicals Calomel
Chancroid	None	Inoculation experiments in human volunteers	Definitive	+	Sulfonamides (Arsenicals still to be tested)
Lymphogranuloma venereum	Unknown probably none	Experimental infection of chick embryo	Probably definitive	+	Arsenicals Sulfonamides
Granuloma inguinale	Unknown probably none	Inoculation experiments in already infected human volunteers	Probably definitive	In process of organization	None as yet

systems provide some protection against gonorrhea and syphilis (subject to the qualifications described above), and probably none against the other three venereal diseases. Satisfactory methods of study are already available as to prophylaxis of all the venereal diseases except gonorrhea, and such studies are actually in progress. Leads already furnished indicate that in the sulfonamides and the arsenicals, alone or in combination, lies a considerable hope of material improvement on present systems, and of the possible eventual replacement of silver salts and calomel by one or both of these two groups of compounds.

V. Methods of study of the prophylaxis of gonorrhea:- There are available five methods of study of the effectiveness of prophylactic agents against gonorrhea. These, with their advantages and drawbacks are listed as follows:-

a) In vitro studies. It is readily possible to determine the gonococcicidal effect of various antiseptics in the test tube; and indeed this is the method heretofore largely relied upon in the introduction of new agents (for packet use). All competent bacteriologists consulted by the Subcommittee on Venereal Diseases agree, however, that in vitro results are not directly translatable to man. The conditions of growth of the gonococcus on the genital mucosa of man cannot be reproduced in the test tube. The toxicity, local and general, of chemical substances for man cannot be so studied. The important time-dose relationship (i.e., the protecting dose and the interval after exposure at which it protects) cannot be studied. The method is of value only as a general screen of chemical substances, i.e., it may be assumed that a substance inert in the test tube will be valueless in man.

Used as a screen, the in vitro method is under study in three laboratories collaborating with the Subcommittee on Venereal Diseases and it has already been demonstrated that both sulfonamides and arsenicals are more effective in vitro than the silver salts now relied upon by Army and Navy.

b) Studies in experimental animals:- Here three avenues of approach are open, as follows:-

1. The effectiveness of prophylactic agents in gonococcal infection of the chorio-allantoic membrane of the chick. Studies of this method have been or are being carried out in two laboratories working under OSRD contract (Bang and Hill); and like the in vitro studies, these indicate that sulfonamides and arsenicals are the drugs of choice. In this method, however, it is difficult if not impossible to separate in vitro and in vivo effect. It is believed that the method can do no more than extend and amplify in vitro studies and that results obtained are probably not directly translatable to man, for many of the same reasons enumerated in paragraph V-a above.

2. The systemic effectiveness of chemical compounds in gonococcal septicemia in mice. This method, also in use, serves as a screen of chemical agents but is obviously inapplicable to the local use of these agents on the genital mucosa.

3. The local effectiveness of prophylactic agents in experimental gonococcal infection of the genital or conjunctival mucosa of animals. To date, this method is wholly inapplicable because no investigator, in spite of years of effort by many, has as yet successfully reproduced such local infection in animals.

Within the past few weeks an OSRD investigator (Hill) has apparently succeeded in producing persistent infection (if not actual disease) in the genital mucosa of mice for as long a period as 18 days. These results, if confirmed in Hill's and other laboratories, may furnish the method of experimental approach to the chemical prophylaxis of gonorrhea, and the experiments should be continued and pushed as rapidly as possible. However, even if amplification and confirmation are forthcoming, it will be several, perhaps many, months before results can be obtained desirable of clinical trial in man. Meanwhile, the problem of gonorrhea and the lost manpower occasioned by it in the Armed Forces is now; and a more rapid and certain answer should be sought.

(c) The treatment of patients already infected with gonorrhea. It may properly be assumed that a chemical substance shown to be curative in already established gonococcal infection will also act as a preventive. This assumption forms the basis of the use of silver salts in present Army and Navy systems, and of oral sulfonamide prophylaxis. The method is being employed as an adjuvent in the present group of studies under the auspices of the Subcommittee on Venereal Diseases. It is, however, open to two major objections:

1) If the local effectiveness of prophylactic agents is under study, it is necessary to withhold from patients so treated a demonstrated method of cure (oral sulfonamides), at a considerable risk of serious complications of the disease to the patient and with a menace to the public health.

2) It fails to permit any definition whatever of the time relationships of prophylaxis to exposure.

For these reasons, the method, like the others so far described, can serve only to screen chemical substances, and to provide relative rather than absolute proof of their efficacy.

(d) The use of different prophylactic substances under actual field conditions:- It has been repeatedly suggested that several different prophylactic systems be tried in parallel at different Army or Navy posts, or at the same post at different times, and that their efficacy be measured one against the other by the venereal disease rate. Indeed, this plan has already been and is now being followed. It is open to two grave objections:-

1) The venereal disease rate can never serve as an absolute or even as a good relative measure of the efficacy of different prophylactic systems. Immeasurable variables prevent. Nothing accurate can be known as to whether personnel limit themselves to a single prophy-

lactic system (e.g., how many men used condoms in addition to taking chemical prophylaxis?). Nothing can be known of the interval between exposure and prophylaxis except the notoriously unreliable statements of the men themselves. Most important, nothing can be known of the actual exposure rate or of the character of those exposures as between groups of men who did and did not take prophylaxis.

These and other considerations make any absolute conclusions drawn from field experience statistically wholly invalid.

(2) Even if some of these objections could be surmounted in a selected highly intelligent military unit, it would be necessary in a planned prophylactic experiment, deliberately to withhold prophylaxis from a control group of men, an entirely indefensible procedure which cannot be medically countenanced, because of the risk of infection with other and more serious diseases than gonorrhea (e.g., syphilis).

(e) Experiments in chemical and chemotherapeutic prophylaxis in human volunteers:- The four methods of study described above in paragraphs V a, b, c, and d are, for the reasons given, incapable of providing an answer to the questions:- What chemical substance is most effective in the prevention of gonorrhea? and what are the optimum conditions for its application? Perhaps one of them, local gonococcal infection in animals, may at some future time provide the answer (insofar as results obtainable in animals are directly translatable to man), but it is to be emphasized that this is uncertain and in the future, whereas our military problem is now.

The human experiment, as outlined in detail in the three proposals for contract now before CMR will, it is believed, provide a definitive answer to the above questions in the shortest possible time; and, since the experiments will be carried out in man, their results are clearly and immediately applicable.

It is believed that military necessity and the impossibility of obtaining the desired results immediately or in the predictable future, in any other manner, justify the use of human volunteers for this purpose.

VI. The desirability of use of prison populations for such human experimentation. Brief consideration suffices to show that the population group employed for such an experiment must be one which can be (a) isolated from contact with the opposite sex during the period of the experiment, in order to prevent the spontaneous acquisition of gonorrhea and the vitiation of the experiment; and (b) under close and constant medical supervision for a minimum period of six months. The latter is necessary to cover a preliminary observation period of 3 weeks (to ensure that volunteers are not in the incubation period of the disease at the start of the experiment, and to determine their freedom from persistent remains of previous infections); an experimental period of at least 3 weeks in those volunteers prophylactically treated and apparently protected (to ensure that infection was actually prevented); and for controls or for those in whom prophylactic treatment failed to protect, an additional period of 3 months for actual treatment of dis-

ease and determination of its cure. The volunteers in question must therefore be medically available under conditions which prevent sexual intercourse, for approximately 6 months.

Several population groups have been considered for this purpose, the advantages and objections of each as follows:-

a) Volunteers from the civilian population. This is obviously out of the question. It would not be possible to obtain volunteers willing to submit to sexual isolation and medical supervision for 6 months; and even if this were possible, the loss of manpower from industry would be undesirable. Moreover, the expense of such a civilian experiment, involving prolonged hospital isolation, would be prohibitive.

b) Volunteers from personnel of the U. S. Army and Navy. Here volunteers could surely be obtained; but the same difficulties as to sexual isolation and loss of time from training or combat duty prevail. About two years ago, the Surgeons General, U. S. Army and Navy, were informally requested by the Subcommittee on Venereal Diseases to organize this experiment in volunteer military personnel. Each replied that he experiment was inexpedient in military personnel.

c) Inmates of institutions for the feeble-minded or insane. This population group has never been seriously considered, since it is clearly undesirable to subject to any experimental procedure persons incapable of providing voluntary consent.

d) Conscientious objectors to military service. This group has been considered only to be rejected. Their numbers are small. Many of them (excepting the members of certain religious sects) are psychologically unstable persons whose cooperation might prove less than satisfactory. The cost of setting up the necessary medical installations would be prohibitive.

e) U. S. Army and Navy military prisoners. This is a possible population group, assuming that their numbers are adequate and that consent of the Secretaries of War and Navy could be obtained. It is believed, however, that many of them are serving sentences too short to provide the necessary 6 months of observation; and that, perhaps nursing a grievance against the Armed Forces, they would represent a psychologically unsuitable group from which volunteers would be few.

f) Inmates of State prisons and City jails. This is the only population group which seems suitable to the Subcommittee on Venereal Diseases. There are certain immediate advantages, as follows:-

1. It is believed that volunteers could be obtained. Experience in Massachusetts (in the blood substitute experiment) and

testimony from elsewhere indicates that many prisoners have not lost their patriotism because imprisoned for crime; and that many are anxious to do whatever and all they can to help win the war.

2. Prisoners are already subject to the necessary sexual isolation.

3. Ample medical facilities are already available, or can be readily and inexpensively expanded, in the prisons chosen.

4. These medical facilities and the enforced sexual isolation make it possible to carry out the entire experiment (unless in exceptional individual cases) on an ambulatory rather than on a hospitalized basis, thus permitting prisoners to continue at work and minimizing both loss of time and expense.

5. Prisoners represent a population group many, perhaps the majority, of whom have already had one or more attacks of gonorrhea, and are therefore aware that the risks of the experiment are small.

VII. The grounds for acceptance or rejection of the proposals by CMR-OSRD. Two questions are involved:- a) the legality of the experiment; and (b) its expediency.

The legal questions involved have already been considered. While there may be local statutes in one or another State which might impede or prevent the experiment in that State, it is nevertheless believed that on a volunteer basis, and subject to a properly executed release by the volunteer, the experiment is entirely legal.

Expediency involves a consideration of the reaction of public opinion. This is entirely a matt r for speculation. The public might react with commendation (as in the case of the Massachusetts prison experiment, the nature of which has not been publicized), with condemnation, or with complete indifference. It is perhaps desirable to point out that a limited human experiment with gonorrhea, involving sexual intercourse between non-infected prostitutes and infected men, and for the benefit of a proprietary remedy with supposed prophylactic and contraceptive properties, was carried out several years ago. This experiment, far more socially objectionable than those herewith proposed, was published in the lay press (in KEN by Paul de Kruif) and in the medical literature (J. Okla. State Med. Soc.). So far as is known, no public protest followed.

The question of expediency has been thoroughly considered by the Subcommittee on Venereal Diseases, National Research Council. It is partly for this reason, as well as for the medical reason that in all probability not enough suitable volunteers may be secured from any one prison, that these experiments are planned in several States, widely distributed geographically. It is almost wholly for this reason that the national backing of CMR-OSRD with the already

secured approval of the Surgeons General, U. S. Army, Navy, and Public Health Service is requested. Whatever political risk may be involved to the elected officials of a given State will be minimized, if not completely avoided, if such experiments are carried out with such national backing and in several States at once.

It is believed that the public has been well educated as to the venereal diseases in the last 7 years; that it is aware of the menace of these diseases to the civilian population as well as to the military; and that it will approve of any sound scientific proposal looking toward improved methods of prevention or cure.

VIII. Recommendation. For the reasons given above, I recommend that CMR-OSRD approval be given to the present (and possibly to future) proposals for contract for a study of chemical and chemotherapeutic prophylaxis of gonorrhea in human volunteers drawn from State and City prison populations.

Very truly yours,

J. E. Moore

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

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