

NIH.08.001059

RG443 NIH-ORG-OC Box 4 Appropriations 2-2



IN REPLYING, ADDRESS THE

FEDERAL SECURITY AGENCY
U. S. PUBLIC HEALTH SERVICE

m Allen

Should we have a
file "Material for
Budget Preparation"
for such material?
VAS

26 May 1947.

804 Medical Arts Bldg.
Baltimore 1, Maryland.

To Members of the Syphilis Study Section
National Institute of Health.

Dear Doctor:

I am notified by the Research Grants Office that it is necessary within the next few days for each Study Section to name a sum desired for the prosecution of investigation in its particular field during the fiscal year 1949 (Beginning July 1, 1948). I am told that these gross over-all estimates will be used by the Research Grants Office in requesting an appropriation from the Bureau of the Budget. I am further told that in a preliminary sense only the over-all estimate is necessary but that within a few days thereafter it will be desirable for the representatives of the Research Grants Office to break down each of the over-all estimates submitted by Study Sections into sub-categories of research within the entire field; and to present some documentation of the desirability of the sums requested for each of the sub-categories.

Since time was of the essence I have taken the liberty of writing Dr. Van Slyke to the effect that the Syphilis Study Section believes that an over-all budget of \$900,000. is desirable for fiscal 1949 for scientific investigation in the field of venereal diseases. I am now under the obligation of breaking this down into sub-categories and of presenting a justification of each. To that end I have reviewed the applications before the Syphilis Study Section from the time of its formation to the present, and have broken down into six categories the studies they represent, as follows:-

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- I. Fundamental Studies in Experimental Syphilis
- II. Fundamental Studies in Experimental Gonorrhea and the Minor Venereal Diseases
- III. Applied Clinical Studies in Syphilis.
- IV. Applied Therapeutic Studies in Syphilis.
- V. Applied Clinical and Therapeutic Studies in Gonorrhea and the Minor Venereal Diseases.
- VI. Statistical Service.

Enclosed herewith is a table listing in three columns the total sums (a) requested of the Syphilis Study Section by applicants in 1948; (b) the total sums recommended for approval; and (c) the total sums tentatively recommended for fiscal 1949.

I also enclose herewith a tentative draft of a letter to Dr. Van Slyke outlining the amounts suggested for each of these categories for fiscal 1949, together with a brief paragraph of explanatory comment concerning each of them.

Would you be good enough to go over these enclosed documents and to write me, if possible by return mail but in any event to reach me not later than June 10, your opinion of the following points:- (a) Does the total sum of \$900,000. seem to you suitable? Do you approve of the manner in which this total sum is divided between the six categories of endeavor listed above? If you have suggestions as to revision upward or downward of these amounts, please give me your revised estimate.

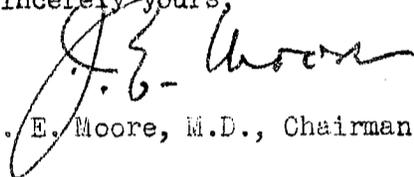
(b) Do you approve of the explanatory comment dealing with each of these sub-categories and, if not, will you suggest editorial revision, deletions, or additions?

Dr. Peterheld

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On receipt of suggestions from all members of the Study Section these will be amalgamated into a final draft of a letter to Dr. Van Slyke, to be available to him for defense before the Bureau of the Budget by June 15th.

Sincerely yours,


J. E. Moore, M.D., Chairman
Syphilis Study Section.

JEM:G

Encl.2

Cc: Drs. Altshuler
Eagle
Heller
Johnson
Mahoney
Mast
Muench
Price
Seeger
Solomon
Stokes
Turner
Van Slyke

Table

	Requested 1948	Recommended	1949 Tentatively recommended
I. Experimental syphilis	\$200,334.59	\$121,922.80	\$260,000.00
II. Exp. Gonorrhoea & Minor V.D.s	Approximately 22,000.00 ⁽¹⁾⁽²⁾	14,479.00 ⁽²⁾	50,000.00
III. Applied clinical Studies Syphilis	144,923.84 ⁽³⁾	137,320.00 ⁽³⁾	250,000.00
IV. Applied therap. studies in syphilis	644,956.08 ⁽⁴⁾	302,487.89 ⁽⁴⁾	250,000.00 ⁽⁶⁾
V. Applied clin. & therap. studies in gc. & minor v.d.	57,393.50	25,056.00 ⁽⁵⁾	60,000.00
VI. Statistical service	27,507.60	22,006.08	30,000.00
Total	1,097,115.61	623,271.77	900,000.00
1) Justina Hill \$15,951.60 C. M. Carpenter about \$6,000.00 2) Does not include Greenblatt (see below) 3) Mahoney \$105,000 (Guatemala); 20,000.00 of Moore's total; Clark 4) Exclusive of cost of penicillin and streptomycin 5) Greenblatt 6) Inclusive of cost of penicillin and streptomycin.			

Please reply to:
 804 Medical Arts Building
 Baltimore 1, Maryland.

May 1947.

Dr. C. J. Van Slyke, Chief
 Research Grants Division
 National Institute of Health
 Bethesda 14, Maryland.

Dear Doctor Van Slyke:

On May 26, 1947, I wrote you indicating that the total sum of money thought to be desirable for the Syphilis Study Section for the prosecution of research in the venereal diseases for the fiscal year 1949 was \$900,000.00.

The Syphilis Study Section believes that this total sum should be allocated as between six broad sub-categories of investigative research, as follows:

I. Fundamental Studies in the Bacteriology, Immunology, and Biology of Experimental Syphilis in Animals.	\$260,000.00
II. Fundamental Experimental Studies in the Bacteriology, Immunology, and Biology of Gonorrhoea and the Minor Venereal Diseases.	50,000.00
III. Applied Clinical Studies in Syphilis	250,000.00
IV. Applied Therapeutic Studies in Syphilis	250,000.00
V. Applied Clinical and Therapeutic Studies in Gonorrhoea and the Minor Venereal Diseases	60,000.00
VI. Biostatistical Service	<u>30,000.00</u>
Total . . .	\$900,000.00

In explanation of these amounts the Syphilis Study Section has authorized the following brief comments:

I. Fundamental Studies in the Bacteriology, Immunology, and Biology of Experimental Syphilis in Animals. The therapeutic experiments of the last decade

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including intensive arsenotherapy and penicillin in the treatment of syphilis, has reemphasized the importance of a large number of unsolved problems in the biology of syphilitic infection. In spite of the mass application of intensive and semi-intensive treatment methods, including penicillin, the results obtainable, both in terms of cure of the individual patient and in public health control of the infection, are less satisfactory than might have been anticipated. With penicillin, as so far used in early syphilis, failure rates range between 25 and 35 per cent.

~~The incidence of syphilis/during the past decade of application of these treatment methods to millions of persons~~ ~~has not fallen~~ ~~but instead appears actually to be~~

~~rising.~~ It seems at least possible that the eventual control of syphilis will depend not on the mass treatment of infected persons, but instead on the application of fundamental knowledge which is so far lacking.

The most important problem in this field is of course the successful cultivation of virulent T. pallidum on artificial media. This is the corner stone to an understanding of the immunology of syphilis. Until the organism is successfully grown, nothing will be known of its chemistry, of the curious and unexplained factors of tissue localization, of the fundamental aspects of immunity, acquired or induced, or of the possibility of control of the disease by immunologic procedures. Many subsidiary problems of the biology and pathology of syphilitic infection, of the response of this infection to therapeutic agents, and of the mechanism of action of these agents, are susceptible of study only in the experimental laboratory. Prominent among these problems are, for example, the development of a completely specific laboratory/^{test}for diagnosis, which will eliminate the confusion caused at present by false positive tests. Corollary to this investigation is the development of a test of cure.

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During 1948, applications totaling \$200,334.59 were presented to the Syphilis Study Section for investigation in the fundamental aspects of experimental syphilis. Of these, applications aggregating \$121,922.80 were recommended for approval to the National Advisory Health Council. ✓

At present there are within the United States nine laboratories capable of contributing materially to experimental studies of this nature. The amount of money which can be profitably expended by each of these laboratories is limited by space. Unlike the acute infections, experiments in the field of syphilis in animals are prolonged, often requiring months or years for completion, and demanding a substantial amount of floor space for the ^{prolonged} housing of such large animals as rabbits and monkeys. Studies of this nature are likewise expensive because of the cost of animals and the personnel needed for their maintenance. Certain of the nine existing laboratories have plans for expansion of floor space. It would be highly desirable if Federal funds could be made available for this purpose. Since provision for buildings is not, however, available through the Research Grants Office, the aggregate sum of \$260,000, appears to be the total amount which under existing conditions can be profitably expended with available facilities.

II. Fundamental Experimental Studies in the Bacteriology, Immunology, and Biology of Gonorrhoea and the Minor Venereal Diseases. Only a relatively small number of laboratories in the country is, at present, interested in fundamental investigations of gonorrhoea and the minor venereal diseases. This is exemplified by the fact that for fiscal 1948, within the field of gonorrhoea, there was requested from the Syphilis Study Section only the approximate sum of \$22,000. for the prosecution of studies in this field. (~~Of the sum requested, \$14,479. was recommended for approval to a single grantee.~~) As to gonorrhoea, the major problems re-

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quire further laboratory investigation dealing with fundamental and applied studies in the bacteriology of the gonococcus, its chemistry and immunology. Desirable also is the successful accomplishment of experimental gonococcal infection in animals in such a manner as to reproduce the clinical features of gonorrhea in man.

Studies in these fields may lead to improved methods of diagnosis, to an experimental study of new treatment procedures, and to the development of adequate tests of cure. They may also elucidate a number of completely unknown points in the epidemiology of gonorrhea.

As to the minor venereal diseases, chancroid, granuloma inguinale, and lymphogranuloma, further laboratory studies are urgently needed for the development of simpler and more accurate methods of cultivation of the ^{causative agents} immunology, epidemiology, and experimental chemotherapy.

III. Applied Clinical Studies in Syphilis. These have been relatively neglected in the last few years because of the pressing importance of a study of improved methods of treatment. The Syphilis Study Section was presented for fiscal 1948 with only ^{two} ~~three~~ applications in this field, aggregating ^{39,923.84} ~~\$14,923.84~~ _{-105,000}.

(a) ~~the Guatemala study dealing with the experimental transmission of syphilis to human volunteers and improved methods of prophylaxis;~~ (b) a study of the constitutional aspects of tabes dorsalis, which may be considered as an investigation into the human immunology of syphilis; and as collateral ^{this,} to the effect of sex hormones in the treatment of certain manifestations of tabes dorsalis; and ~~(c)~~ (d) studies in the epidemiology of syphilis in an effort to differentiate more clearly between reinfection and relapse.

There remain, however, a substantial number of unsolved problems. For example, material has now accumulated in a number of the large clinics in the count-

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ry, a study of which will permit a more accurate definition of the period of infectiousness of syphilis; of the question of strains of spirochetes, of the effect of pregnancy on syphilitic infection, on the pathology of syphilis and its relationship to mortality; of the evolution of syphilitic heart disease, and of the causes of certain of the serious and hitherto unexplained manifestations such as interstitial keratitis. In addition are desirable retrospective studies of various treatment systems analyzed by the newer biostatistical methods, in order to form a base line of comparison for penicillin or other new treatment agents to be introduced.

The aggregate of the sums recommended for approval by the Syphilis Study Section for fiscal 1948 for studies falling within this general category, was \$137,320. Recommended for fiscal 1949 is the total sum of \$250,000.

IV. Applied Therapeutic Studies in Syphilis. For the past four years, under the auspices of the Committee on Medical Research and the Research Grants Office of the National Institute of Health, a nation-wide study of the effect of penicillin in syphilis has been in progress. Because of lack of funds, it was necessary to terminate, as of June 30, 1947, that part of the nation-wide experiment dealing with penicillin in early syphilis. This was done in spite of the fact that the available evidence so far indicates that penicillin, though suitable for mass application, is unsatisfactory for the individual patient, since failure rates of 25 to 35 per cent occur. It seems essential to continue the penicillin experiment both in early syphilis and in various other stages of the infection, though on a somewhat reduced basis. A large reduction in scale has already been accomplished on the basis of experience of the past four years. Eliminated from further support have been those clinics with a poor record of performance, either in terms of examination and treat-

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ment of patients, or in terms of their ability to follow treated cases in order to observe the results. Improvements are constantly occurring in penicillin itself; and there is reason to believe that other antibiotic agents will develop which, on the basis of laboratory evidence, justify their trial in human beings. The cooperative organization of clinics as now established, should so far as possible be held together, in order that a final and definitive answer concerning penicillin may be obtained; and that new and improved agents may be tried as they develop in the laboratory.

For fiscal 1948 the Syphilis Study Section was presented with applications for a continuation of the penicillin study aggregating \$644,956.08. Recommended for approval from this sum was the aggregate of \$302,487.89. (This latter sum was exclusive of the cost of penicillin and of streptomycin for therapeutic trial in lymphogranuloma). The cost to the Research Grants Office of these drugs for fiscal 1948 is estimated to be approximately \$50,000., thereby increasing the aggregate amount expended during fiscal 1948 to approximately \$350,000.00.

In consideration of the contraction of the penicillin experiment which has already taken place, and of the further contraction which may be expected during the next eighteen months, on the basis of the information accumulated within that period; and in further consideration of the partial transfer of interest of certain of the cooperating clinics from the therapeutic study to applied clinical studies (see Paragraph III above), the amount suggested for fiscal 1949 for applied therapeutic studies in syphilis is \$250,000., inclusive of the cost of penicillin.

Epidemiological

V. Applied Clinical and Therapeutic Studies in Gonorrhea and Minor Venereal Diseases. As to gonorrhea, unless there develop penicillin-resistant strains

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of the gonococcus, the advent of penicillin has provided a quick, safe, and practically certain method of cure of this disease. Having in mind previous experience with the sulfonamides, however, it is essential to determine that penicillin-resistant strains of the gonococcus do not develop; and in the event that they do, to conduct further therapeutic experiments with alternative agents.

As to the minor venereal diseases, therapeutic studies during fiscal 1947-48 have indicated the value of streptomycin in the treatment of granuloma inguinale. Further therapeutic studies are, however, essential in the field of lymphogranuloma venereum - a serious and relatively widespread disease in the southern States. Likewise necessary are clinical studies of the epidemiology of chancroid and of the transmissibility of granuloma inguinale and of lymphogranuloma venereum and the clinical aspects of the latter disease, particularly in regard to its relationship to ulcerative proctitis and colitis.

In fiscal 1948 the Syphilis Study Section was presented with applications in this field aggregating \$57,393.50. Approved was a single application in the amount of \$25,056. Recommended for fiscal 1949 is the sum of \$60,000.

VI . Biostatistical Service. In the course of the nation-wide penicillin study there has been created in the Johns Hopkins School of Hygiene and Public Health a Central Statistical Unit which has undertaken the analysis of the penicillin material from cooperating clinics. The amount requested for fiscal 1948 in support of this Unit was \$27,507.60. Recommended for approval was the amount of \$22,006.08. Estimated for fiscal 1949 for the activities of this Unit is \$30,000.

Sincerely yours,

J. E. Moore, M.D., Chairman,
Syphilis Study Section.

JEM:G

Table

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IV. Applied therap. studies in syphilis	644,956.08 (4)	302,487.89 (4)	250,000.00 (6)
V. Applied clin. & therap. studies in gc. & minor v.d.	57,393.50	25,056.00 (5)	60,000.00
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C. M. Carpenter about	\$6,000.00		
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4) Exclusive of cost of penicillin and streptomycin			
5) Greenblatt			
6) Inclusive of cost of penicillin and streptomycin.			

144,923.84
105

39,923.84

137,320
105,000

32,320.00