

History of O.S.R.D.

April 6, 1945

Dr. James P. Baxter, III
Historian
O.S.R.D.
1530 P Street, NW
Washington, D. C.

Dear Dr. Baxter:

I enclose herewith the Committee
on Medical Research material which has been pre-
pared for your use in the compilation of the
history of the O.S.R.D.

Very truly yours,

Chester S. Keefer, M. D.
Medical Administrative Officer

cc: Dr. Stewart

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REPRODUCED AT THE NATIONAL ARCHIVES

7/15/45

*Sent to
Dr. Board*

COMMITTEE ON MEDICAL RESEARCH

To meet the ever increasing medical problems of global war, the Committee on Medical Research has continued its research activities in the prevention and treatment of diseases which are encountered in troops throughout the world. The problems are numerous and complex, and cover a wide range of subjects. One of the additional functions of the Committee on Medical Research is to investigate the conditions under which men may operate at the most effective level under conditions of rapid change in the environment. Physiological adjustment consistent with efficiency is often not possible without the use of some mechanical aid. This is especially true in the field of aviation medicine. Medical Research then covers a large field and is planned to solve the problems which are encountered among military personnel.

In the field of aviation medicine, careful studies and analysis of crash injuries have lead to an improvement in the design of the cockpit -- this has resulted in reducing the number of injuries from crash. These investigations are continuing for the purpose of improving the design of cockpit arrangements, instrument panel layouts, and personal emergency equipment. Other investigations have included the development of protective devices against gravity, decompression sickness.

The use of blood plasma, and blood serum albumin have proved to be very effective in the resuscitation of the wounded -- indeed in many instances these products have been life saving. There are many wounded men, however, who need whole blood. Blood banks had to be set up by military hospitals in the field but a great problem was to preserve blood so that it could be used for a period as long as seven days after bleeding.

Preservatives were developed under the O.S.R.D. which permit blood to be used as long as 21 days after bleeding -- this is a great advantage. Now blood can be withdrawn in this country and shipped by air to foreign theaters of operation at regular intervals, and used at the front many thousands of miles away and many days after bleeding.

One very difficult problem confronting neurosurgeons who operate on patients with head wounds is the control of bleeding from the brain and its coverings. Also, wounds of the skull and brain frequently leave defects in the outer covering of the brain known as the dura mater. From blood plasma, two substances can be isolated, one that will control bleeding from the surface of the brain (fibrin foam) and another (fibrin film) which can be used as a substitute for the dura mater. These blood derivatives have aided the neurosurgeon greatly in his work and are entirely new developments from O.S.R.D. contractors.

Still other materials have been derived from blood plasma and are useful in preventing epidemic diseases such as measles and epidemic hepatitis. Both of these diseases are of great military importance. The gamma globulin fraction from blood plasma can be injected into exposed persons in small volume with most favorable results. This program has opened up entirely new fields of research which will have far reaching effects in the future.

It is widely recognized that many animals and insects serve as reservoirs of disease in man. The body louse transmits typhus fever and relapsing fever; the rat serves as a reservoir for plague and some forms of typhus fever; the mosquito transmits malaria and filariasis; and the mite, scrub typhus; the sand fly, sand fly fever and leishmaniasis; the house fly transmits dysentery. It is not surprising, therefore, that great efforts have been made to discover new insecticides, and new rodenticides. A new rodenticide has been developed by O.S.R.D. that is extremely effective against a variety of rats that are extremely destructive to food supplies and that cause plague. Effective insecticides have also been discovered against lice, mites, sandflies and houseflies. From the use of these new agents in the war against insects and rodents, a great reduction in the incidence of malaria, typhus, dysentery and other diseases of military importance has resulted. Every effort has been made, therefore, to eliminate these infectious agents at their source.

Penicillin continues to exceed our highest hopes as a powerful agent in the treatment of many infections, including wound infections, infected burns, venereal diseases, pneumonia, meningitis and streptococcus infections of the throat. It has succeeded in many cases where the sulfonamides have failed. The research and development of this substance from the laboratory to its present stage was encouraged from the beginning by O.S.R.D. No other agent has done so much for so many diseases.

One of the greatest problems in military medicine throughout the world is malaria. While there are effective agents available for suppressing this disease, there are no drugs available that will either prevent or cure the infection. Being able to suppress the disease only delays the appearance of its symptoms. The greatest problem of all comes with the return of troops from infected areas because this is the time when they develop symptoms of their disease. Up to the present there is no cure available for relapsing vivax malaria. Great strides have been made in controlling the mosquito with insecticides and proper drainage of land. As a result of the extensive studies by O.S.R.D., the best methods of using (atabrine) quinacrine as a suppressive and therapeutic agent were developed and defined for the first time since its discovery. This has resulted in saving untold numbers of days of non-effectiveness in the armed forces.

It has been demonstrated conclusively that quinacrine is superior to quinine. Quinine is not a curative agent for vivax malaria so that great efforts have been and are continuing to be expended upon a search for an agent that is better than quinacrine, and one that is a true prophylactic and a curative agent. An example of the magnitude of the problem might be stated as follows: If 500,000 men have relapsing vivax malaria, then one can say that each man will average about 5 relapses, and each relapse may require 5 hospital days. These relapses may recur over a period of months. This would mean 12,500,000 hospital days to take care of this group of patients alone. While the goal in the search for a prophylactic and curative agent has not been reached, there are promising leads. The program is being pursued with great energy because of

the magnitude and importance of the problem.

In view of the prevalence of tropical diseases in regions where warfare is being waged, there has been an intensification of the study of ways and means of preventing cholera, bubonic plague, Japanese B encephalitis, dysentery, leishmaniasis, schistosomiasis. New information has emerged and is being applied promptly.

As the war progresses the importance of convalescence and rehabilitation of the sick and wounded becomes increasingly important. A number of investigations are under way which have as their objective the shortening of the period of convalescence and the speeding up of the period required for rehabilitation. This study includes not only those disorders which follow battle wounds but also those which result from battle or combat fatigue. These investigations are time consuming, and long term projects. Fortunately, new information of practical value is being obtained all of the time.

The Committee on Medical Research has shifted the emphasis on their programs of research from time to time depending upon the medical needs and problems in global war. They have had the full cooperation of the Army, Navy and Public Health Service in these efforts at all times.

History of CDR Dr. Andrus

February 25, 1946

MEMORANDUM

To: Dr. Chester S. Keefer

From: E. Cowles Andrus, M. D.

Subject: CDR Long History - Your Memorandum February 12, 1946

As requested in your memorandum of February 12, there is given below the outline being followed by Division I in the preparation of its portion of the CDR history:

Chapter I	-	Introduction	-Dr. E. Cowles Andrus
Chapter II	-	Infectious Diseases	-Dr. A. R. Dochez Dr. James E. McCormack
Chapter III	-	Venereal Disease	-Dr. J. E. Moore
Chapter IV	-	Tropical Disease	-Dr. Lucille R. Farguhar
Chapter V	-	General Medicine, with Special Consideration of Problems of Convalescence	-Dr. E. B. Bay Dr. John E. Howard Dr. E. Cowles Andrus

We expect that secretarial expenses will not exceed \$250.00.

Suggested by Dr. Keefe and Division Chiefs

PART I - MEDICINE

Chapter I - Infectious Diseases

Section I - Bacterial Diseases

Cholera
Dysentery
Salmonella

Hardy
Hardy
Hardy

Section II - Viral and Rickettsial Diseases

Influenza
Encephalitis
Typhus

Stanley
Stanley
Stanley

Section III - Fungal Diseases

Allylamine
Tuberculosis
Streptococcus

Forstall
Waring
Swift

Section IV - Parasites

Meyer

Section V - Sex Diseases

Adams

Section VI - Miscellaneous

Ascaris
Ultraviolet
Adjuvants
Antibiotics

Bigg
Levinson
Harris
Keefe/Anderson/Wood

Chapter II - General Diseases

Section I - Chemotherapy

Stokes

Section II - Immunology

Eagle

Section III - Molecular Gene Therapy

Hain

Section IV - Serology (Imp. Animal and Man)

Hill

Chapter III - Tropical Diseases

Section I - Amebiasis

Farghar

Section II - Bilharziasis

"

Section III - Chagas' Disease

"

Section IV - Leishmaniasis

"

Section V - Malaria Infections

Kearny

Chapter IV - Nutrition and Rehabilitation

Section I - Nutrition

Howard

Section II - Stimulation

Starr

Section III - Neuromuscular

Overholser

Section IV - Psychological Aspects

Section V - General Health

Section VI - Physical Therapy

Section VII - Mental Health

Section VIII - Vocational Training

Section IX - Social, Economic, and Cultural

Section X - Physical Examination

Section XI - Laboratory Tests

Section XII - Special Investigations

Section XIII - Prognosis

Section XIV - Summary of the Course

History of OSRD-CMR

January 23, 1946

Dr. J. Earle Moore
 804 Medical Arts Building
 Baltimore 1, Maryland

Dear Earle:

This is to give you in somewhat greater detail the plan which I mentioned for the section of the OSRD history to be devoted to the activities of the CMR. I appreciate very much your willingness, busy as you are, to tackle the section on venereal disease. This particular history is planned to be directed to scientists who are not necessarily professional specialists. Someone has used the simile for the chemical volume that it "should be similar to what might be given in an after-dinner speech at a chemical society meeting."

The overall plan suggests that each chapter include:

- a. A statement of the objective and the reasons for trying to reach it.
- b. An account of the means undertaken to reach the objective.
- c. The principal results obtained - whether positive or negative, whether successful or unsuccessful.
- d. The significance of the results (if any) - and the suggestions for future work (if discernible).

The section on venereal disease would describe the OSRD-sponsored investigation in:

- a. Gonorrhea in experimental animals and man.
- b. Prophylaxis of venereal disease.
- c. Biologic false positive serologic tests in syphilis.
- d. Penicillin in syphilis.

The publication schedule which has just come to my attention calls for the manuscript to be in the office of the Chairman of CMR not later than May 1. That is the date which you mentioned to me. I hope it will not put you to too much trouble. Incidentally, the present plans call for 50 pages, 300 words per page, for the section on venereal disease. If, in your opinion, this is not enough, please let me know.

Yours sincerely,

E. Cowles Andrus, M.D.
 Chief, Division of Medicine

SUGGESTED OUTLINE FOR PORTION OF OMR HISTORY ALLOTTED TO
DIVISION OF MEDICINE

- Chapter I. Introduction - Dr. Andrus 3-5pp
- Chapter II. ✓ Infectious Disease - Dr. Dochez (CMM & McC) 30pp
Outline for this chapter will be submitted *
by ARD soon, to which add 1 subsection on
Mycotic Infections (McC) 1-2pp
- Chapter III. ✓ Venereal Disease - Dr. Moore 25pp
JEM earlier suggested following plan,
suitable as outline here:
- a. Gonorrhoea in experimental animals and man - Hill
 - b. Prophylaxis of venereal disease - Eagle
 - c. Biologic false positive serologic tests
in syphilis - Rein
 - d. Penicillin in syphilis - Stokes
(section (d) would constitute the bulk
of the chapter)
- Chapter IV. ✓ Tropical Disease - Dr. Farquhar 15pp
This chapter should include something of the
nature of the disease, the magnitude of the
problem, the threat remaining after the war;
also a mention that a few "tropical diseases"
are discussed elsewhere, e.g., under Infectious
Diseases and Division on Malaria, and that con-
tributions of Insect Control Division are
contributions against tropical diseases.
(bishmaniasis, amebiasis, filariasis, schistosomiasis)
- Chapter V. ✓ General Medicine - Dr. Andrus, et al 30pp
(Special orientation toward Convalescence)
- a. Metabolic aspects - Howard & Andrus 10pp
 1. Hematologic aspects- McCormack & Andrus 2pp
 - b. Cardiovascular system - Bay & Andrus 8-10pp
 - c. Psychologic aspects - Andrus 8pp
- Chapter VI (or separate division) Chemotherapy and Antibiotics - Keefer 20pp
(Include antibiotics for tuberculosis -
CMM) 2pp

1/22/46

PREFACE

A. H. Richards
 Chairman, Committee on Medical Research

In this and the following volumes are recounted the results of a great cooperative effort in medical research, conducted by the Office of Scientific Research and Development (OSRD) in the interests of our national defense. Written in so far as practicable in nontechnical language, it constitutes a report to the public of advances in medicine which, although primarily designed to promote the health and welfare of our armed forces in camp or in the field, cannot fail to accrue to the permanent advantage of our civilian population. The report is necessarily incomplete and lacking in technical detail; the definitive records will be found in the medical and scientific journals and in scientific monographs. Already more than 1300 papers describing specific aspects of the work have been published and hundreds more will appear in months to come.

It is perhaps to be regretted that it has not been deemed possible ^{in these chapters} in this history to assign credit in the text to all individuals for their contributions, but this omission is consistent with the fact that our country was in danger and with the unselfishness with which physicians and scientists were ardently eager to be used in our national effort.

A ^{short} account of the organization and administration of the Committee on Medical Research (CMR) can be found in the volume on the administrative history of the OSRD. It has seemed, however, not only appropriate but essential for clear understanding of the circumstances attending its efforts to include in this preface a brief description

CHAPTER 3VENEREAL DISEASES

For expert advice regarding the urgent problem of control and treatment of venereal disease, the armed services turned to the National Research Council and specifically to its Subcommittee on Venereal Diseases. As phases of this problem were identified that required further research, projects were sponsored by the Committee of Medical Research in various institutions with a view to advancing the knowledge of the prevention and treatment of these diseases.

There are five so-called venereal diseases usually transmitted by sexual contact: chancroid, lymphogranuloma venereum, granuloma inguinale, gonorrhea, and syphilis and gonorrhea. On the other hand, in certain areas to which members of the armed forces were dispatched the other venereal diseases, particularly chancroid, are much more prevalent. In the light of this fact it became imperative that proper measures for prophylaxis be developed against as many types of venereal disease as possible. *Chemical Prophylaxis of Venereal Disease and Related Studies.*

At the beginning of World War II the same system of chemical prophylaxis had been in use in the United States Army and Navy for about thirty years. This had been devised largely on clinical grounds. It consisted of initial urination (theoretically in order to wash out gonococci from the urethra) thorough washing with soap-and-water (theoretically to prevent chancroid and syphilis) the intraurethral injection of mild silver proteinate (theoretically to prevent gonorrhea) and the inunction of the parts with 33.3 per cent calomel ointment (theoretically to prevent syphilis). The adoption of these several steps in the old Army

prophylactic system was based on scientific information only in respect of the use of calomel ointment for the prevention of syphilis. Earlier and not altogether satisfactory studies had suggested that soap-and-water was prophylactically effective against both chanroid and syphilis. The possible value of calomel ointment in the prevention of syphilis had been inferred from the original experiments of Hetschikoff and Roux and by subsequent studies in experimental animals carried out by Nichols, Walker, Mahoney, and others. The use of silver proteinate for the prevention of gonorrhoea rested on no other foundation than that it appeared to be of some value in the treatment of established gonococcal urethritis. Nothing was known of possible prophylactic agents against granuloma inguinale or lymphogranuloma venereum.

The estimate of the value of the whole prophylactic system rested entirely on poorly controlled and relatively unconvincing statistical studies carried out in the field. There was some reason to believe that if applied within one hour following exposure it might be of value, but this had not been definitely proved. A systematic study of prophylactic agents against the several venereal diseases was therefore carried out both in animals and in man.

Chanroid

The prophylaxis of chanroid was investigated in two different clinics - at New York University and at the University of Virginia. Various prophylactic agents were tried in volunteers deliberately inoculated with chanroid. These studies showed that soap-and-water was of no value, but that sulfonamides locally applied in an ointment

base or in vanishing detergents were effective in preventing the development of chancroidal infection. The ideal drug and concentration thereof appeared to be 15 per cent sulfathiazole, incorporated in an ointment base. There was some evidence that the combination of sulfathiazole and calomel was more effective against chancroid than sulfathiazole alone. These studies eventually led to the incorporation of 15 per cent sulfathiazole in the prophylactic ointment finally adopted by the armed forces.

Lymphogranuloma Venereum

Studies looking toward the possible development of a prophylactic agent against lymphogranuloma venereum were carried out primarily in the Squibb Institute for Medical Research. First it was shown that the virus could be propagated on the chorioallantoic membrane of the chick embryo. Efforts were made to adapt this experimental method to a study of prophylactic agents. Owing to the limitations of the method itself, these were not entirely successful. So far as could be determined, however, none of the drugs tested exercised any prophylactic effect against this disease. Efforts were made to produce experimental infection in animals comparable to that in man, with the hope that prophylactic agents could be tried out in vivo, but these attempts too were unsuccessful. As matters now stand, there is no information concerning the prophylaxis of lymphogranuloma venereum.

Granuloma Inguinale

The causative organism of granuloma inguinale had been successfully cultivated by Anderson of Vanderbilt University, again in the yolk of developing chick eggs. This discovery was confirmed by Hake of the

Squibb Institute, working under an OSRD(CMR)* contract. However, efforts to establish experimental granuloma inguinale in animals or in human beings were unsuccessful, and there appeared to be no suitable method of testing prophylactic agents. As with lymphogranuloma venereum, therefore, no information indicative that this disease can be prevented by chemical prophylactic means has been developed.

Gonorrhea

At the beginning of these studies no satisfactory method existed of evaluating prophylactic agents against gonorrhea. Some hint of their value was gained by the local action of various compounds in established gonococcal urethritis. Studies of the local effect of the installations of sulfocamide ointment into the urethra of patients with already developed gonorrhea did not indicate that this method was likely to be effective in the prevention of the disease.

Efforts were therefore directed to establishing gonococcal infection in experimental animals, which had never previously been successfully accomplished. These took two directions. First, Justina Hill at the Johns Hopkins Hospital attempted to establish gonococcal infection on the vaginal mucosa of the immature female mouse. Second, C. Philip Miller, of the University of Chicago, undertook to establish gonococcal conjunctivitis or ophthalmia in

*This abbreviation is used throughout to designate contracts made by the Office of Scientific Research and Development on recommendation of the Committee on Medical Research.

the eye of the rabbit. Hill succeeded in establishing the temporary persistence of gonococci, if not actual infection. This was accomplished only after carefully testing a number of expedients calculated to lower the resistance of the host. None of these appeared to be successful in establishing genuine gonorrhoeal vaginitis, and though with certain methods a high proportion of the animals showed persistence of viable gonococci for periods of forty-eight to seventy-two hours. Since actual gonococcal infection was apparently not established, the method did not lend itself to accurate study of chemical prophylactic agents. Nevertheless, Hill did survey the effect of a large number of prophylactic agents and demonstrated that, within the limitations of the method employed, 33 per cent calomel ointment was indestructing gonococci locally. Silver proteinate also gave promising results. Sulfonamides and a number of other salts of silver and mercury that were investigated seemed to be ineffective.

Hill has published certain papers dealing with the development of her method (see Bibliography), and in addition has prepared at the request of the Committee on Medical Research two comprehensive surveys of the literature dealing with experimental gonococcal infection in animals and with experimental gonorrhoea in man.

Miller, by means of the injection of virulent gonococci into the aqueous or vitreous of rabbits' eyes, finally developed a method that produced actual persisting infection for a period of many weeks in a high proportion of animals. An effort was made to study the effect of prophylactic agents introduced within the globe of the

eye following such experimental infection. The results are scarcely applicable to the prevention of gonococcal urethritis, but are particularly significant with regard to the chemotherapy of this infection.

Finally, confronted by what appeared to be the insuperable difficulty of producing gonococcal infection in experimental animals within the period of the war and in time for this to be of value to the armed forces, an experiment was organized to study the production of experimental gonorrhoea in male human volunteers. This was carried out by Mahoney and his associates of the United States Public Health Service with the cooperation of the Federal Bureau of Prisons in the the federal penitentiary at Terre Haute, Indiana. A team of investigators was sent to Terre Haute and somewhat over 200 volunteers were employed. Efforts were made to produce experimental gonorrhoea in these volunteers by almost every conceivable expedient except by the intraurethral inoculation of pus taken directly from the cervix or urethra of infected females or by the natural method of infection - sexual intercourse. The former method was avoided because of the possible danger of transmitting syphilis simultaneously

The results of this study (see Bibliography) indicated that it was not possible to produce experimental infection with any degree of regularity, either by the use of cultured gonococci of many strains or by direct patient-to-patient transfer of pus from natural or experimental gonorrhoea in males. Only about half the volunteers became infected. It seems probable that this duplicates the epidemic situation in nature. There is reason to believe that, for reasons not clearly defined, not all men exposed to an infected woman will become infected.

Since experimental gonorrhoea could not be produced with any degree of regularity in volunteers, this method likewise did not lend itself to a study of chemical prophylactic agents. The study did, however, demonstrate that resistance to sulfonamides was an inherent property of the strain of gonococci employed. When volunteers were infected with a strain of organism previously known to have been sulfonamide-resistant in vivo, with sulfonamide resistance further demonstrated in vitro, all the infections produced were likewise sulfonamide-resistant, requiring penicillin for cure. On the other hand, when experimental infection was produced with a sulfonamide-susceptible strain, it could always be readily cured with sulfathiazole.

The net result of these experiments in chemical prophylaxis against gonorrhoea was nil so far as any practical application during the period of the war was concerned. It is still unknown whether any prophylactic agent, including the silver proteinate that the armed forces have used for thirty-five years, has any value in the prevention of this disease.

Syphilis

The primary need for study in the chemical prophylaxis of syphilis was to define more clearly the effect of calomel. Investigations looking to this end were carried out in a number of different laboratories, particularly those of Chesney and Eagle at Johns Hopkins and of Fleming at the University of North Carolina. It was shown that in the dosage used in man, 4 gm. of a 85 per cent calomel ointment, corresponding roughly to 200 mg. of calomel per kilogram of body weight, the preparation did have some effect in preventing the experimental infection in

mental infection in rabbits. It was demonstrated that the efficacy of calomel was dependent in part on particle size. So-called "microsized" calomel ointment, with a particle size of 1 micron or less, was much more effective than the cruder preparation previously employed by the Army, which contained particles up to 100 micra in diameter.

The results were also considerably influenced by the ointment employed. The problem of ointments was investigated in a number of different laboratories, particularly those of Calvery of the Food and Drug Administration, Thompson of the Warner Institute for Medical Research, Bake of the Squibb Institute for Medical Research, and Chesney. A large number of ointments - three hundred or more - were studied in experimental animals with particular attention and to the absorption of drugs contained therein to such factors as primary irritation of skin and mucous membranes. The results stimulated the further trial of a new ointment combining 55 per cent calomel with 15 per cent sulfathiazole. This ointment, in a vanishing cream base, was pharmaceutically much more acceptable for general use than the greasy lanolin ointments previously employed. The studies of the prophylactic effect of calomel in experimental animals likewise confirmed the original impression of Mahoney that calomel ointment exerted not only a local but also a systemic effect in prophylaxis.

Since the efficacy of calomel ointment in the prophylaxis of syphilis could not, however, be established with absolute certainty, other studies were undertaken by Eagle and Mahoney on the effectiveness of arsenic applied in solution or in ointment bases. These studies in-

icated that phenyl arsenoxides were much more effective than calomel in the prevention of experimental syphilis in animals and that their action was purely local rather than systemic. It was likewise demonstrated that in the concentrations employed in experimental animals these arsenical drugs were not irritating or apparently sensitizing in man. Unfortunately, the experimental information became available so late in the war that opportunity for extensive field testing of arsenic-containing preparations was not possible. Such a trial will be carried out in further experiments by the United States Public Health Service.

Summary of Results. From the theoretical standpoint, the results of these investigations were in a sense disappointing. The major achievements were the demonstrations that soap-and-water was not effective against chancroid but that sulfathiazole in ointment would protect against it, and that arsenic was superior to calomel in the prevention of syphilis in experimental animals. No agents effective in preventing granuloma inguinale or lymphogranuloma venereum were developed. Likewise no information was provided as to the effectiveness of any substance in the prevention of gonorrhoea.

From the practical point of view, however, the information outlined above did permit the adoption by the Army of a new single-tube "Prokit" containing 15 per cent sulfathiazole and 30 per cent calomel in a vanishing-cream base. This was easier of application than station prophylaxis or the two-tube prophylactic kit previously employed. Such inconclusive evidence as is available from field trials suggests that if either have any effect the single-tube "Prokit" is fully as effective as station prophylaxis in the prevention of venereal disease. The demonstration of the usefulness of penicillin

in the treatment of gonorrhoea is described elsewhere. It is worth emphasis here that the availability of this antibiotic agent with a rapid curative effect in this disease, and without the hazard of toxic side effects, was responsible for the prompt restoration to active service of thousands of men.

Treatment. By far the most important problem faced by the Army in the field of venereal disease was the selection of sufficient and safe methods for the treatment of syphilis and the organization of their administration. In the early acute phases the patient is not ill or disabled. The principal purposes of treatment are to prevent him from infecting others and to prevent manifestations of the disease.

From 1492 to 1945 progress in the treatment of syphilis had been slow and hesitating and the results incomplete and inconclusive. Until 1909 all treatment of this disease was empirical, and the only really useful information that emerged concerned the efficacy of mercury in some cases. This had survived as the single important ingredient in the medieval treacles and other compounds administered over four hundred years.

Arsenic in its various forms, beginning with Ehrlich's discovery of "606" in 1909, had since then been administered by physicians more or less by trial and error. With a few outstanding exceptions, no successful attempts had been made to follow cases for long periods after treatment, and no series of cases of adequate size had been studied sufficiently to yield definitive information. It has to be

emphasized that to measure the influence of any therapeutic procedure on the course or outcome of syphilis requires that the case be observed for months or even years. Unlike such diseases as pneumonia, in which the brilliant results of chemotherapy are apparent within a few hours or at most a few days, syphilis is a chronic disease. A patient apparently cured today may for unpredictable reasons relapse nine months later.

The Subcommittee on Venereal Diseases of the National Research Council assembled the available information regarding the various methods suitable for application in the treatment of syphilis under military circumstances. They recommended that infected persons undergo a course of treatment lasting twenty-six weeks and composed of forty injections of Mapharsen and sixteen of bismuth. All forms of arsenic treatment of syphilis have a significant mortality rate owing to the poisonous effects of this chemical. In the opinion of the committee, no reasonably safe system of arsenic treatment had been evolved that could be administered in less than twenty-six weeks. Attempts to administer therapeutically adequate quantities of arsenic within a few days had been accompanied by a prohibitive percentage of complications, some of them fatal.

Under OSRD(CMR) contracts attempts to discover more efficacious and less toxic compounds of arsenic were continued. Other investigators without such contracts but in close collaboration cooperated with the Subcommittee on Venereal Diseases and the Committee on Medical Research in an extensive study of intensive arsenotherapy in experimental syphilis of animals. From this investigation there emerged a number of significant facts. First, the toxic dose of arsenic, as

exemplified by Mapharsen and its analogues, was directly related to the time period of its administration: the shorter the interval within which a given amount of treatment was compressed, the higher was the mortality rate in the experimental animals treated. Second, and conversely, the curative dose of arsenic, again as exemplified by Mapharsen and its analogues, was approximately the same within the limitations of the experiments, regardless of the total period of administration. Whether the drug was administered by means of a single massive intravenous injection, by intravenous drip over a period of several days, or by interrupted injections at various time intervals, extending up to a total treatment period of six weeks, the curative dose in experimental syphilis in rabbits was about 7 mg. per kilogram of body weight.

These two facts made it entirely possible to state that there was no optimum method of treatment of early syphilis utilizing arsenic as the drug in question. Faced with the desirability of administering a total dose of, for example, 7 mg. per kilogram, the time period over which this dose was administered determined the safety of the treatment. With these facts in hand it became possible to predict mortality rates in rabbits that were translatable with extraordinary fidelity to human beings. In both rabbits and man it became clear that the administration of a curative dose of arsenic within a period of ten days or less yielded a mortality rate of approximately 1 in 200. Most, if not all, of the deaths in man occurred because of toxic encephalopathy, the incidence of which was about double the death rate. The mortality rate could be decreased to any desired level, and practically to the point of

of disappearance, by spacing individual treatments in such a manner as to prolong the total period of administration.

These considerations influenced the Subcommittee on Venereal Diseases to advise the armed forces against the use of intensive arsenotherapy by means of the so-called "five-day" treatment or intensive modifications thereof and this form of treatment was not utilized in the armed forces in this country. In combat areas, on the other hand, and particularly in the European Operations, a modification of intensive arsenotherapy was developed requiring twenty days for completion. This was carried out in a substantial number of patients with a comparatively low risk.

The combined experimental studies in rabbits and clinical studies in man likewise demonstrated a third significant point: that the curative dose of arsenic in man was approximately three to five times that in the rabbit. Whereas the latter dose was approximately 7 mg. per kilogram of body weight, that in man ranged between 20 and 35 mg., requiring the administration of a minimum of 1200 mg. of Mapharsen (or an analogue) to the average 60-kilogram man with early syphilis.

A fourth point of major importance was developed both in experimental and in clinical studies; namely, that the addition of bismuth to arsenic exercised an apparently synergistic effect and improved the results obtainable with either drug alone.

An additional point of interest, although not of major practical import, was brought out by studies in the experimental laboratory. It was here demonstrated that when arsenic (Mapharsen) was administered to animals during induced fever, its toxicity was approximately doubled but its therapeutic efficacy was increased about fourfold. As corollary to this study another was carried out in which distribution of arsenic in the tissues

was determined following its administration at normal body temperatures.

The twenty-six-week treatment system was employed by the armed forces until the middle of 1944, when it was replaced by treatment with penicillin. A preliminary analysis of the results of this system has recently been made in an unpublished paper by Lieutenant Colonel Thomas Sternberg and Major William Leifer. This study of 3000 cases indicates that the twenty-six week treatment system was extremely satisfactory, producing an over-all failure rate in early syphilis in the Army of approximately 5 per cent. The mortality rate was roughly 1 in 30,000. It is estimated that from 200,000 to 300,000 men were treated in the Army and Navy by this system, with results superior to those previously attained by any treatment system in civilian life.

The Treatment of Arsenic Intoxication with Bal (British Anti-Lewisite). In collaboration with the Committee on War Cases of the National Research Council, the Subcommittee on Venereal Diseases fostered experimental and clinical studies in the use of Bal (2-3-dimercaptopropanol) in arsenic poisoning. It was demonstrated that experimental animals could be protected against lethal doses of arsenic by the administration of Bal simultaneously with or shortly after treatment. It was also shown that the administration of Bal enormously increased the urinary output of arsenic applied in the treatment of arsenic poisoning in human beings. It has likewise been shown with reasonable conclusiveness that Bal is of value in the treatment of arsenical toxic encephalopathy and of post-arsenical dermatitis. The mortality rate from arsenical toxic encephalopathy, which, without the use of Bal, appears to be 50

per cent or greater, can probably be reduced to 20 to 25 per cent by the use of this product. In a substantial number of patients with post-arsenical dermatitis treated with the drug, either by ointment or parenterally, there were no deaths, and the duration of illness seemed to be materially shortened.

As a result of these studies, Bal was distributed to large syphilis-treatment centers, both in the armed forces and in civilian communities in the United States.

Effect of Penicillin. In June, 1943, Mahoney, Arnold, and Harris at the United States Marine Hospital on Staten Island demonstrated in experimentally infected rabbits and in 4 human beings that penicillin exercised a prompt and powerful effect on the organism of syphilis, bringing about the destruction of the organism in open lesions, with consequent healing, and reversal of positive serologic reactions. In view of the fact that penicillin is almost completely innocuous to man, even in enormous doses, this was a valuable discovery.

At this time, owing to the shortage of penicillin and the urgent and extraordinary need for it for the treatment of battle casualties and serious acute infections in the armed forces, it was decided that the available supply of the drug should be devoted not to a large-scale human experiment but to the further study in the experimental laboratories of Mahoney and of Eagle of the effect of penicillin in rabbit syphilis. Within three months, however, the supply of penicillin had greatly increased, and the results from these laboratories were so encouraging that in September and October, 1943, steps were taken to arrange for large-scale human trial. The cooperation of the Army, Navy, and United States Public Health Service was promptly enlisted to set up experimental treatment centers in various

installations of these services. In addition, over twenty-five civilian institutions engaged in the study under OSRD (CMR) contracts.

The pressing need of the armed forces was for information regarding the effect of penicillin in early syphilis, and secondarily for knowledge regarding its usefulness in latent syphilis and neurosyphilis. It was nevertheless decided that while the major efforts should be centered on these phases of the infection, the investigation should not neglect to explore the value of penicillin in the treatment of other stages of the disease.

There was organized under the Subcommittee on Venereal Diseases what was called the Penicillin Panel, which included representatives of the Army, Navy, United States Public Health Service, Committee on Medical Research, Subcommittee on Venereal Diseases, and Committee on Chemotherapeutic and Other Agents. In this panel the design of the experiment was discussed and developed and from time to time evaluated.

It was evident that so far as early syphilis was concerned there was presented an unparalleled opportunity for quantitative study of the effect of penicillin. It was arranged that all cooperating institutions, governmental or civilian, should select their patients on a uniform basis, examine the cases, and record information concerning the history and physical findings in a uniform manner. They were to apply treatment schemes prescribed by the Penicillin Panel, follow the patients so far as possible in an identical fashion, and record the results of all these observations on specially designed forms, which to be forwarded to the Central Statistical unit for analysis. This was established in the Department of Biostatistics of the John Hopkins School of Hygiene and Public Health, under the direction of

Dr. Lowell J. Reed,

The original effort was to evaluate the time-dose relation - ship had been used in the first 4 patients treated by Mahoney. The method of administration of penicillin was to give it in aqueous solution by the intramuscular route, with a three-hour interval between injections. The total dose arbitrarily chosen (without previous experience or any guidance from the experimental laboratory) was 1,200,000 units and the duration of treatment (again arbitrarily chosen) was set at seven and a half days. The method of administration and the interval between injections were based on pharmacologic evidence that had by that time accumulated in the general use of penicillin. It was decided at the beginning to hold these factors constant, and to determine the relative effects of total dosage within the range of 60,000 to 9,600,000 units and those of total time of administration within the range of four to thirty-two days. The dosage steps were as follows: in 60,000, 300,000, 600,000, 1,200,000, 2,400,000, 4,800,000, and 9,600,000 units. The total duration of treatment was increased in the same manner; that is, four, eight, sixteen, and thirty-two days, with variation as to dose in each time interval. Likewise to be explored in human beings were the combination of penicillin with other chemotherapeutic agents - for example, arsenic, bismuth, and fever therapy and a study of absorption-delaying methods of administration of the drug.

Simultaneously with these clinical studies in early syphilis, a group of six cooperating laboratories of experimental syphilis was organized under the direction of a subcommittee of the Penicillin Panel, composed of Dr. Harry Eagle (chairman) and Drs. Mahoney, Chesney, and Rake. These laboratories were to study the optimum

method of administration of penicillin in early and late syphilis of rabbits.

The experimental and clinical studies in early syphilis accumulated valuable information. It was demonstrated in experimental animals that the C. D. 50* of commercial penicillin administered in twenty to twenty-four injections every four hours day and night for a four-day period was 1500 to 2000 units per kilogram of body weight and that the C. D. 95 ** was about 3000 units per kilogram. It was further shown that the curative dose of penicillin was a function of the combination of total dose, duration of treatment, and frequency of injection. When penicillin was combined with arsenic in treating rabbit syphilis, there was a synergistic effect, so that the curative dose of each drug when the two were administered simultaneously was approximately one fourth the curative dose when either one was given separately. It was also shown that penicillin in experimental syphilis was more effective at fever temperature than at normal body temperature.

In the human experiments it became obvious that, within the time periods assigned for total duration of treatment, that is, from four to eight days, any total dosage less than 1,200,000 units was relatively ineffective and that a total dosage of 1,200,000 units administered within either four or eight days produced an apparent-cure rate in early syphilis approximating 80 per cent. This information was sufficiently satisfactory by the spring of 1944 to justify a recommendation

*The amount necessary to cure 50 percent of infected animals.

** The amount necessary to cure 95 percent of infected animals.

by the Subcommittee on Venereal Diseases on April 20 that penicillin be substituted for arsenic and bismuth in the treatment of syphilis in combat areas, and June 29 it was recommended to the Army and Navy that this drug be adopted throughout both services in all of operation for the treatment of early and latent syphilis. On the basis of information then available, the treatment plan advised for both early and latent syphilis was 2,400,000 million units of penicillin administered by the intramuscular route in divided doses every three hours day and night to a total of sixty injections in seven-one half days. This treatment plan was adopted by the armed forces at a slightly later date, and from that time until April 1946, over 250,000 patients in the Army and Navy with early and latent syphilis were so treated.

In the meanwhile, data concerning the treatment of early syphilis in human beings have continued to accumulate in the Central Statistical Unit, so that at present records of some 20,000 cases are available for study. These cases include patients treated by about thirty different treatment schedules - some with penicillin alone, others with penicillin and fever, and a substantial new group treated with penicillin by an absorption-delaying method, the drug being suspended in a mixture of peanut oil and beeswax.

It has become obvious from the human study that any kind of treatment scheme of early syphilis requires a minimum of two years for evaluation. For this reason it is not possible at present to make definitive statements with regard to any total penicillin dosage larger than 2,400,000 units nor to compare the periods of total duration of treatment beyond the limits of four to fifteen days. Within these limits, however, the human study has been shown that the results

are apparently equally satisfactory whether the total duration of treatment is four, eight, or fifteen days. The results improve progressively with increased dosage, but the magnitude of difference in percentage of favorable outcome tends to diminish as dosage is stepped up. With 2,400,000 units of penicillin administered in eight days, the system employed by the armed forces, the failure rate within the first year is approximately 15 per cent. Failure or success cannot be estimated by original effect in terms of disappearance of treponemes, healing of lesions, or serologic reversal, since the results are essentially identical in respect of these factors, regardless of total dose. Failure can only be measured by the incidence of relapse, either clinical or serologic (including reinfection) and by seroresistance at the end of one year after treatment. It is the time required for accumulation of such data that makes it necessary for a given treatment system to have been followed for a minimum of twelve to twenty-four months before the results can be determined.

The experiment in the treatment of syphilis in human beings likewise indicates that the administration of arsenic with penicillin improves the results as compared with penicillin alone; the same is true of penicillin and bismuth. It is not yet clear whether penicillin and fever is better than penicillin alone, although the present indication is that this combination is not effective in man. Sufficient time has not yet elapsed to form any conclusion with

respect to the value of absorption-delaying methods of administration of penicillin in the treatment of syphilis.

While a 15 per cent failure rate from 2,400,000 units of penicillin in eight days is considerably greater than the failure rate under the best available methods of treatment with arsenic and bismuth (metal chemotherapy), which is in the neighborhood of 3 to 5 per cent, the advantage is still with penicillin. With the latter drug all patients can be treated, whereas with arsenic and bismuth, which for safety require a minimum of twelve and a maximum of twenty-six weeks of treatment, a substantial proportion of patients either do not complete the required course or, take treatment irregularly over a much longer period of time. To the extent to which arsenic and bismuth are not given by a regular schedule or a total course of treatment is completed only in part, the results are substantially less good than the 3 to 5 per cent failure rate mentioned above. Moreover, penicillin has the inestimable advantage of freedom from toxicity. No deaths from its use have been reported, whereas metal chemotherapy by any system carries with it a mortality rate that although of course capable of adjustment, cannot be reduced below a probable 1 in 30,000 patients treated.

In other forms of syphilis the results of penicillin therapy, as determined from the nationwide study, may be briefly outlined as follows.

Prevention of prenatal syphilis in infants. The most successful application of penicillin in the treatment of syphilis has been in preventing the development of congenital syphilis by treatment of infected pregnant mothers. Over 500 pregnant women with early syphilis have now undergone treatment with this drug. More than 95 per cent

of the infants have been born alive and free from infection. In the remaining relatively small number of failures, the reason for failure is usually readily determinable, and it seems entirely possible that by recognition of such reasons and the application of re-treatment during pregnancy when necessary congenital syphilis may eventually be eliminated with entire safety to the mother.

Infantile congenital syphilis. Penicillin has been used in the treatment of 250 to 300 infants born with congenital syphilis. The dosage scales have been roughly comparable to those used in adults and have been chosen on the basis of an appropriate number of units per kilogram of body weight. At present the recommended total dose of penicillin for infants is between 100,000 and 400,000 units per kilogram, administered over a time period of eight to fifteen days. The results have been fully as satisfactory as those in adults, and in some respects more so. The mortality rate, always high in infantile congenital syphilis, is certainly no higher than with earlier methods of treatment and is not ascribable to the treatment itself. There is a lower incidence of clinical relapse in penicillin-treated infants than in adults, and serologic reversal now appears to be equally frequent.

Latent syphilis. Although a large number of patients with latent syphilis have been treated with penicillin in the armed forces, no attention has been paid to this problem in civilian clinics, and no definite statements can be made regarding the effect of the drug. The results of any form of treatment in this stage of the infection are measurable only by serologic response on the one hand or by eventual clinical outcome on the other. Before the advent of penicillin it was already clear that these two factors bore no

not be determinable for a number of years.

Cardiovascular syphilis. What has been said of latent and benign late syphilis applies even more to cardiovascular syphilis. Determination of the efficacy of any therapeutic system requires the treatment of a large number of patients who are not subsequently re-treated if the original treatment effort seems to have been unsuccessful and who are followed from treatment until death. The efficacy of treatment is measured only partly by relief of symptoms but principally by prolongation of life expectancy beyond that of untreated patients. For these reasons an organized study of the effect of penicillin in this stage of the infection has not yet been that therapeutic shock (the Jarisch-Herxheimer reaction)* to penicillin may prove to be a matter of major importance. Certainly the experience of the past suggests that powerful treponemicidal drugs should be given cautiously in this group of patients. Preliminary information indicates that the initial doses of penicillin should not exceed 1000 units and should be increased gradually, probably over a five-day period, to full therapeutic doses.

*This is the only important reaction occurring after the use of penicillin in syphilis. It is apparent in all stages of syphilitic infection. It is usually manifested by fever appearing within the first twenty-four hours of treatment, ranging in height from 99.5 to 105° F., persisting for a few hours, and then disappearing. In patients with obvious lesions as, for example, in early syphilis, this febrile reaction is frequently associated with a temporary intensification of the lesions previously present. The reaction occurs in about 75 per cent of all patients with early syphilis and in a substantially smaller proportion of those with late syphilis. It has no clinical significance except in cardiovascular syphilis, where, theoretically at least, it may produce serious damage, and in certain forms of neurosyphilis, especially paresis, where convulsive seizures, especially paresis, where convulsive seizures, vascular accidents, and so forth have apparently been precipitated by the incautious use of initial large doses of the drug. Here it seems desirable to avoid it. This can usually be accomplished by the administration of small doses for a day or two.

Interstitial Keratitis. This distressing ocular lesion of late congenital syphilis responds to penicillin only in irregular and unpredictable fashion, and to about the same extent as has been previously observed with other methods of treatment.

Neurosyphilis. One of the outstanding achievements of penicillin has been to reduce the incidence of asymptomatic neurosyphilis among patients treated in the early stages of syphilis. When untreated, from 15 to 40 per cent of such patients may be expected to develop spinal-fluid abnormalities within the first two years; with penicillin treatment this percentage is reduced to 2 per cent or less.

A large number of patients with various types of neurosyphilis have been treated with penicillin. These types have ranged from the asymptomatic variety, in which the diagnosis hinges solely on routine examination of the spinal fluid, up to and including the most serious manifestations of the disease, that is, tabes dorsalis and general paralysis of the insane. It has been shown that the drug administered either intravenously or intramuscularly exerts a profound effect, in spite of the fact that it does not apparently penetrate into the nervous tissue or into the spinal fluid in appreciable concentration.

The favorable effects of penicillin treatment of neurosyphilis are most obviously reflected in the changes in the spinal fluid. Without exception, elevated cell counts and protein content return promptly to normal, sometimes within the actual period of treatment and in practically all cases within a month thereafter. Other spinal-fluid abnormalities, including a positive Wassermann reaction and an abnormal colloidal gold curve, respond more slowly, but there is a continuing favorable effect that persists for at least the present duration of the experiment, about two years. This favorable effect occurs in all types of neurosyphilis.

From the clinical point of view it is more difficult to evaluate the effect of the drug because of the extraordinarily protean character of neurosyphilis. On the whole, however, it appears that penicillin is more efficacious in the treatment of any type of neurosyphilis than chemotherapy with arsenic and bismuth. It appears to be less effective than fever therapy with induced tertian malaria. There has, however, been an accumulation of evidence that the combination of fever therapy with simultaneously administered penicillin may be more effective than either treatment method alone. It is fortunate in this respect that penicillin exercises no therapeutic effect on malaria, thereby permitting its continued administration during malarial therapy. The information so far accumulated permits the hope that the treatment of any type of neurosyphilis may be completed with the combination of fever and penicillin therapy within four to six weeks, thereby obviating the prolonged additional period of chemotherapy that has been customary in the past. The evidence in this respect has been sufficiently convincing so that the Army and Navy have adopted the routine of fever and penicillin treatment in their various neurosyphilis centers.

The Changing Character of Penicillin*

Information concerning the chemical nature of penicillin itself and of the several substances composing commercial penicillin was withheld during the war. Nevertheless, information began to accumulate

*See also pages 000 - 000

by personal communication from a variety of sources to the effect that penicillin, as commercially supplied, is composed of four different penicillin fractions - G, X, F, and K. These fractions differ from each other chemically only in the side chain structure attached to the basic nuclear molecule. They also differ from each other for their potency in vitro against Staphylococcus aureus, penicillin G and F having a potency of 1667 U./mg., X a potency of 900 - 950 U./mg., and K a potency of 2300 u/mg.

There were increasive indications that penicillin as commercially supplied by different manufacturers contained varying amounts of these several fractions and, indeed, that the amounts might vary in the product of the same manufacturer from time to time. Eventually it became clear that penicillin as originally supplied in 1943 and early in 1944 contained predominantly penicillin G or a mixture of G and F. At some time during 1944 the drug industry generally substituted a strain of penicillium chrysogenum for P. notatum. This, together with various modifications adopted in the culture of the mold and in the purification of the final product, resulted in the appearance in commercial penicillin of substantial amounts of penicillin K.

Commercial penicillin has also during the nearly three years conduct of the syphilis experiment changed markedly in another respect; that is, in increasing potency against S. aureus in vitro, in terms of units per milligram. As originally supplied, the potency of commercial penicillin was about 200 u/mg., whereas at present it is 900 to 1400 u/mg. This purification has resulted in a decrease in the amount of impurities present and regards these impurities certain suggestions had begun to appear in the literature to the effect that

penicillin of low potency and therefore containing a high proportion impurities might possibly be more effective in various respects than more highly purified or crystalline penicillins. Leads in this direction were obtained in experimental syphilis in rabbits, in the action of crude and purified penicillin against sarcoma cells in tissue culture, and in the similar action of such substances against streptococcal infections in mice and against the development of sea-urchin eggs in vitro.

Early in 1945 the Penicillin Panel of the Subcommittee on Venereal Diseases, recognizing that experimental studies of penicillin fractions G, X, F, and K and of the impurities present in commercial penicillin should be carried out, made efforts without success to obtain crystalline penicillin in preparations containing a high proportion of impurities. Eventually, arrangements were made with pharmaceutical houses for supplies of penicillin species, and small quantities were obtained of crystalline G, X, and K and slightly larger quantities of impure (90 per cent or more) F and K. These fractions were distributed among six laboratories of experimental syphilis, which undertook to examine them on a cooperative basis.

About the middle of February, 1946 it was reported from two of these laboratories penicillin that K was ineffective in syphilis of the rabbit in the largest dose employed; that is, 16,000 u/kg. Simultaneously it was shown that G was fully as effective as commercial penicillin as supplied early in 1944. The C.D. 50 of penicillin G and of this earlier commercial penicillin was in the order of 1500 to 2000 u/kg. It therefore appeared that penicillin G was at least ten times as effective in experimental syphilis of animals as penicillin K. Information regarding the relative efficacy of penicillins X and F in this disease is not yet available. Almost simultaneously with the

demonstrated inefficacy of penicillin K, information developed that in human beings commercial penicillin, as supplied since mid-1944, was not as effective against as the products supplied before that date. These two facts seemed almost certainly to be related and prompted a further exploration of penicillin K as contrasted with other penicillin fractions.

It has been shown in several laboratories that the inefficacy of penicillin K is probably not due to any lack of intrinsic bactericidal power, but instead depends on the pharmacologic fact that, unlike penicillins G, X, and F, penicillin K is in large part rapidly destroyed in the animal or human body. It has also been shown that penicillin K is from 1/17 to 1/6 as effective as penicillin G in streptococcal and pneumococcal infections of mice.

Biologic False-Positive Serologic Tests. Before and during the war mass blood testing was adopted by industry, in hospitals, and by law in premarital and prenatal examinations. Later the Selective Service performed blood tests on all draftees. These conclusively demonstrated an unexpected number of biologic false-positive serologic fractions for syphilis, caused by a variety of different conditions. For example, in malaria a biologic false-positive serologic reaction appears at some time during the course of the acute illness in 100 per cent of cases. Following vaccination for smallpox the incidence is about 20 per cent, and this same incidence prevails during or after a number of acute infections including infectious mononucleosis, atypical virus pneumonia, mumps, acute upper-respiratory conditions, including the common cold, and various other infectious diseases particularly prevalent in the armed forces.

Information began to accumulate indicating that most normal human

beings possess in their blood serum a tiny quantity of reagin or a reagin-like substance, demonstrable by various special technics but so small in amount as under normal circumstances not to interfere with serodiagnostic tests for syphilis. It was likewise indicated, however, that about 20 per cent of the normal population were probably potential reactors in the sense that under the influence of an extraneous stimulation, such as the virus infections mentioned above, this substance, normally present in infinitesimally small quantities, might increase in quantity to such a point as to interfere with standard serodiagnostic tests and to provide biologic false-positive reactions. It was likewise suggested by clinical evidence arising from American Red Cross blood-donor centers that the mere donation of a large quantity of blood on one or several occasions might produce a temporary biologic false-positive reactions.

The frequency with which such reactions occur and the high incidence of extraneous stimulating factors, both in the civilian population and within the armed forces themselves, made it desirable to conduct a series of investigations on fundamental factors related to the production of these reactions and their differentiation from the positive blood reactions characteristic of syphilis.

As one step in this investigation an effort was made in a prison population deliberately to produce biologic false-positive reactions by repeated blood donations. This experiment, carried out on a small scale, gave negative results. It did not, however, disprove the possibility that blood donation might in a certain very small proportion of cases be an exciting factor.

Another investigation was devoted to a study of the serologic pattern produced in various stages of syphilitic infection and in patients with known or suspected false-positive blood reactions. In addition, efforts were made to evaluate two so-called "verification tests," especially that proposed by Kahn. This study demonstrated that there was no constant serologic pattern which could be utilized to differentiate true from false positive reactions and that the verification tests, including that of Kahn, were of no value. It was shown that the verification phenomenon formerly assumed to prove or disprove the fact of syphilis depends instead on the reagin titer of the serum in question. In patients with high-titer serums, whether due to syphilis or to some other cause, the Kahn verification tests gives results of the so-called "syphilitic type." Conversely, with low-titer serums, again whether due to syphilis or to some other cause, this test usually provides results of the so-called "biologic type."

An extensive physicochemical study of the phenomenon of biologic false-positive reactions has been carried out by Neurath at Duke University. He has shown that reagin produced by syphilis is associated with a G-2 fraction of globulin. He has discovered several characteristics that promise to lend themselves to serologic differentiation between true and false positive reactions. The most important of these is that the serologically active euglobulin fraction prepared either electrophoretically or chemically from false positive serums has a higher titer than the whole serum, whereas with serums from patients with syphilis the titer of this fraction is comparable to or less than that of the whole serum. Second, it has been shown that the addition to the isolated globulin fraction of heat

stable serum inhibitor prepared from the crude serum albumin fraction causes complete inhibition of the former's activity in the case of false-positive reactions whereas with serums from patients with syphilis only partial inhibition, or none at all is observed.

Applying these criteria to a large number of serums from patients with proved syphilis, proved false-positive reactions, and normal serums, it has been shown that from 90 to 99 per cent of all serums from patients with syphilis give a syphilitic type of reaction, whereas from 90 to 99 per cent of all false-positive reactors give a characteristic differential reaction. Studies are now in progress under other auspices to determine the nature of the inhibitor; its source, and the mechanism of inhibition by serum albumin.

RG 227, OSRD, CMR, General Records, 1940-1946
No title / other identifying information available