

# COOPERATIVE CLINICAL STUDIES OF THE TREATMENT OF SYPHILIS IN THE UNITED STATES

by R. A. VONDERLEHR, M.D.<sup>1</sup>

**I**N 1927 the Health Section of the League of Nations planned a study of the various problems which relate to the treatment of syphilis. Five American clinics<sup>2</sup> consented to cooperate in this investigation. Believing that their clinical material provided information on many points not emphasized by the study outlined by the Health Section and desiring to extend the investigation to various forms of late as well as early syphilis, they organized a cooperative clinical group whose function was to conduct a retrospective inquiry into the results of treatment in the several stages of syphilis. The cooperation of the United States Public Health Service with its coordinating and statistical facilities was enlisted. The cost of these studies was considerable and was borne, first, by a grant obtained from an anonymous donor, and later by the Milbank Memorial Fund. Within the past year the United States Public Health Service has assumed the entire burden of completing them. The support of such organizations has made it possible for the United States to conduct an independent evaluation of the treatment of syphilis in its representative clinics and, in addition, extend the desired cooperation to the League of Nations.

## PLAN AND PURPOSE

The American study had as its aim the analysis, interpretation, and evaluation of pooled records from the five syphilis clinics. The intention was to utilize the results of this composite experience to simplify and standardize methods and practice in the

<sup>1</sup>Passed Assistant Surgeon, United States Public Health Service.

<sup>2</sup>The American clinics selected were the Johns Hopkins University Clinic headed by Doctor Joseph Earle Moore; the Mayo Clinic by Doctor Paul A. O'Leary; the University of Michigan by Doctor Udo J. Wile; the University of Pennsylvania by Doctor John H. Stokes, and the Western Reserve University Clinic by Doctor H. N. Cole. The cooperation of the United States Public Health Service was sought in the administrative management of the studies and for its statistical facilities.

treatment of syphilis for the information of the specialist and the guidance of the doctor in general practice. Aside from the greater value resulting from the fusion of the records, it has been possible to reflect in these studies the opinion and experience of the participating clinicians.

The accumulated clinical material of these five clinics approximated 75,000 records of patients treated for syphilis. Uniformity of selection of cases has prevailed. The extent of this selection will be stated later in a brief description of the findings from the various studies. Several scientific papers based on these cases have been published. These relate to the treatment of early syphilis, the problem of mucosal and cutaneous relapse, the treatment of latent syphilis, the effects of syphilis in pregnancy, and the reactions of the human body to the arsenical compounds administered in the treatment of this devastating disease. Additional articles are in the process of preparation on the treatment of early syphilis, and plans for an analysis of the results of the treatment of syphilis of the cardiovascular and central nervous systems are under way. With the material now available every important aspect of syphilis can be covered except one—the prenatal. It is now proposed to collect records from the cooperating clinics pertaining to the treatment of prenatal syphilitic infection.

#### PRACTICAL VALUE OF THE STUDY

The great prevalence of syphilis and the large number of cases in any community make it economically impossible for health organizations with existing appropriations to give the consideration to the problem which is commensurate with its size. Under present medical organization in the United States it is the practicing physician who holds the most prominent position in the program for the ultimate eradication of syphilis. In view of this fact, the results of the studies made by the cooperative clinical group have been widely distributed among the members of the

medical profession. The findings, when applied, should go far in solving the syphilis problem.

The studies are not only of interest to the physician engaged in private practice, but they are also of inestimable value to the health officer because they place in his hands informative material for physicians regarding the most modern and authoritative procedures in syphilis therapy. Indeed, if all of the information uncovered were applied, the syphilis problem would soon be solved. Among the impediments in the way of the application of the findings the foremost one is the high cost of an intelligent program against syphilis. Without such a program the present penuriously financed measures will be largely ineffective. Another handicap is the indifference with which the average infected person regards the disease. Progress is further hindered, though to a limited degree, by the failure of many physicians to keep well informed on the subject and to adopt new methods, the apathetic and disinterested regard of the problem by most health officers, and the opprobrium and disrepute for people who contract syphilis, fortunately now somewhat decreasing but formerly strongly entrenched in the public mind.

The prevention of the spread of infection by treatment has been reemphasized in the cooperative clinical studies, and a standard plan of therapeutic procedure evolved which insures favorable results.

The primary purpose of this paper is to summarize and, as far as possible, to present in nontechnical language the most important findings which have resulted from the collective studies that have thus far been completed.

#### EARLY SYPHILIS

The studies in early syphilis give the most hopeful indication for the suppression of syphilis both as an individual and a community problem.

The need of a system for the application of antisyphilitic remedies, which will insure the best results and possibly ultimate cure, has long been felt. The cooperative clinical studies have demonstrated that the most satisfactory treatment of early syphilis must be *continuous*; it must employ an arsphenamine and bismuth, the latter intramuscularly; it must call for not less than twenty, and unless special resistiveness is encountered, hardly more than thirty injections of the arsphenamines; and, the system should call for continued treatment with heavy metal for one year after all symptoms and signs of the disease have disappeared. Blood tests should be taken at least at the beginning and end of each arsphenamine course, and the patient should be warned of the lack of significance of the negative report from the standpoint of the schedule.

The reappearance of weak positive blood reactions, after negative tests have appeared, should be taken as seriously as strong or fully relapsing positives. A spinal fluid examination with Wassermann, cell count, protein estimation, and colloidal gold test should be made before the end of the arsphenamine phase of treatment, or before the introduction of any rest period (none to be allowed until after the first year). It is understood that such a system can be carried through only when the patient is able to take these drugs without suffering a serious reaction, and this tolerance should be conserved in every possible way. The same system should be employed whether treatment is begun in the primary stage, without or with a positive blood test (seronegative or seropositive primary), or in the secondary stage.

An analysis was made of 3,244 cases of early syphilis under observation for a period of six months or more. It was found that eight out of every ten of these patients who had a relapse to a communicable form of the disease had received less than fifteen doses of arsphenamine with the accompanying heavy metal. Thirty-five per cent of such relapsed patients had received less

than five doses of arsphenamine. Additional factors demonstrated that the critical time for treatment of the syphilitic patient is in the first two years of the disease. During the first six months after treatment ceased, 45 per cent of the infectious relapses had occurred; by the end of the first year, 73.6 per cent; and by the end of the second year, 91 per cent.

*Results of Treatment Depending on Stage of Disease at Beginning.* Authorities have divergent opinions as to the time, during the early syphilitic infection, when treatment should be started. The development of a generalized immunity to the germ of syphilis in the secondary stage is well known. Some specialists believe that treatment should not be commenced until an opportunity has been given to the patient for the development of this immunity. In other words, when a patient presents himself in the primary stage, especially after a positive blood test has developed, the attending physician gives no immediate treatment but waits for the secondary stage.

A study of the stage of the disease at which the patient began treatment yet subsequently developed an infectious relapse presented a possible solution of this question. It was found that of the primary cases with negative blood reactions 16 per cent showed evidence of infectious relapses, 20 per cent of the primary cases with positive blood reactions, and 9.5 per cent of those patients who began their treatment in the secondary stage of syphilis. It is especially to be noted, however, that the patients who began treatment in the secondary stage of the disease had already passed through a communicable period in the chronology of the disease (the primary stage). During their primary stage 100 per cent of the cases had already been infectious. Thus for the greatest effectiveness in controlling the transmission of the disease it is obviously necessary to begin treatment in the primary stage, with negative or positive blood reactions. This more than outweighs the greater probability that the individual may relapse

if treatment begins early than would be the case if begun in the secondary stage.

*The Relation Between Blood Reaction and Relapse.* The significance of changes in the serologic reaction of the blood in syphilis has long been under investigation by both syphilologists and serologists. In the cooperative clinical studies, among cases which failed to give a negative blood Wassermann reaction after treatment, there was a higher percentage of relapses to the communicable form than among cases in which the Wassermann reaction changed from positive to negative. Under continuous treatment only 2.5 per cent of the patients whose serologic reactions became negative within the first year of the disease developed a mucocutaneous relapse. This compared with 6.7 per cent of those similarly treated whose reaction failed to reverse within the first year. A similar phenomenon was noted with each of the other types of treatment; intermittent, 8.2 per cent and 15.9 per cent; irregular, 12.8 per cent and 42.2 per cent.

It was established that the failure of serologic tests of the blood to reverse was more a matter of how treatment was given than of how much. The regular administration of arsphenamine and heavy metal, especially in the first three months of the disease, caused the greatest number of serologic reversals; even a little treatment given continuously was found to be more than twice as effective as when it was given intermittently.

*Duration and Method of Treatment.* The question next arises as to how long and in what manner treatment is to be given in order to obtain best results from the standpoint of the patient. For the prevention of the late and crippling manifestations of syphilis the advantage of adequate treatment, that is, more than twenty doses of arsphenamine, as compared with inadequate treatment, is evident. There were three times as many individuals who developed some type of central nervous system involvement among those who had received less than twenty doses of arsphenamine.



mine with its accompanying heavy metal than among those receiving more than this amount. The effectiveness of adequate treatment in preventing the development of syphilis of the heart and blood vessels was not noted to the same extent (0.9 per cent adequately and 1.2 per cent inadequately treated). There appeared to be no indications that the development of a cardiovascular or central nervous system involvement depended on the stage of early syphilis at which the patient began treatment.

An effort was made to determine the probability of progression after the patient had remained under treatment for a two-year period or more. It was found that with a continuous scheme of treatment in which an arsphenamine with accompanying heavy metal was used, if the patient began treatment in the seronegative primary stage, 86.4 per cent satisfactory results<sup>3</sup> were attained. But when the same scheme of treatment was used in the early secondary stage, the good results dropped slightly to 81.5 per cent. It is of interest to note that the most effective scheme of treatment in the seropositive primary stage was an intermittent scheme. This may have been due to the fact that these patients gained an immunity in the interim when no treatment was given. Such a hypothesis would coincide with the theory of the development of immunity when treatment is not given until the secondary stage has been reached. In any event, it is important to note that the occurrence of communicable manifestations of syphilis is obviated in the seropositive primary stage by the intermittent system.

From these data it would at first seem advantageous to the patient to delay treatment until he arrives at the early secondary stage. When all types of relapse are reviewed, however, it is found that, aside from the increased number of infectious relapses, there

<sup>3</sup>"Satisfactory result" implies that the patient has been followed for two years or more and that during one probationary year he has had no symptoms of syphilis, his blood has been consistently negative, he has had a negative physical examination and in almost all instances a negative spinal fluid examination, or without these negative findings he has had a reinfection.

is no evidence that the beginning of treatment at any time in the primary stage predisposes the patient to late and crippling manifestations of syphilis. With persistence in treatment any patient with primary syphilis may expect as satisfactory an outcome as is attained by those individuals who wait until the secondary manifestations of syphilis have developed. From a public health standpoint, the grave epidemiologic consequences of delayed treatment have already been discussed and are at once obvious. The cooperative clinical group recommend, therefore, that treatment of early syphilis be instituted as soon as possible, after the appearance of the chancre.

#### SYPHILIS IN PREGNANCY

The findings having the next greatest public health significance relate to those in which the disease coexists with pregnancy. They indicate that with early and adequate treatment during pregnancy the prognosis is most favorable for the birth of an infant apparently free from syphilis. Unfortunately, there are as yet no records available relative to the development of syphilis in the child subsequent to birth. When treatment of the syphilitic mother was adequate, that is, consisted of ten or more injections of one of the arsenical compounds and accompanying heavy metals, and the administration was begun before the fifth month of pregnancy, nine out of ten of all children delivered were apparently non-syphilitic. But, when treatment was delayed until after the fifth month of pregnancy, only a little more than one-half of the children were born alive and nonsyphilitic although the maximum amount of treatment possible in the remaining gestation period had been given.

*Effect of Treatment in Previous Pregnancies.* Treatment even in a previous pregnancy seemed to influence favorably the outcome of subsequent pregnancies. Thus, if treatment had been given in previous pregnancies and not in the last, an apparently healthy child was delivered in the last pregnancy of almost two-



thirds of the women having a negative serologic blood reaction. But where treatment had never been received for syphilis and the blood reaction was negative, only a little more than one-fourth of the women were delivered of apparently nonsyphilitic children. The lesson to be learned is, therefore, perfectly clear and the cooperative clinical group conclude that the syphilitic mother should be given early and adequate treatment throughout every pregnancy whether her serologic test for syphilis gives a positive or negative reaction. One of the most encouraging findings in the study was that women, who had previously had two or three abortions and subsequently received antisyphilitic treatment of any kind, were able to bear living children three out of four times.

*Tolerance of the Pregnant Woman to Treatment.* Does the physiologic state of pregnancy render the human female more susceptible to the toxic properties of the antisyphilitic drugs? On the contrary, these studies demonstrated that the pregnant syphilitic woman was a good risk for arsenical therapy. She tolerated the arsenicals better than the nonpregnant woman. The findings gave evidence that crustaceous dermatitis and icterus, both serious complications to treatment, were more common in the syphilitic woman never pregnant. Such severe reactions as aplastic anemia, purpura hemorrhagica, and death due to treatment were not reported in the pregnant women undergoing treatment.

#### LATENT SYPHILIS

The fact that the average latent case of syphilis has passed the second year of the disease, and that syphilis in this stage does not ordinarily occur in a communicable form makes a consideration of latent syphilis of less significance for the health officer than for the doctor in private practice. The possible prevention of the transmission of syphilis by a latent syphilitic pregnant woman to her offspring offers the most important public health aspect of this stage of the disease. The infectiousness of the semen of the

latent syphilitic male appears to be relatively of less importance though at the present time the degree of such infectiousness is not certainly known. On the other hand, the studies under consideration offer some hopeful signs for the person with latent syphilis, and have resulted in the accumulation of information pertaining to the complex problem of treatment which should be of great value to the practicing physician.

The aim of treatment in latent syphilis is to decrease the probability of clinical progression or relapse in comparison with the results attained when no treatment is given, and to increase the probability of cure or arrest. In addition, treatment should be directed toward the control of the potential infectiousness of a latent syphilitic. Of those patients with latent syphilis treated for from two to five years, ultimate satisfactory results were attained in 46 per cent; from five to ten years in 60.6 per cent; and, of those patients who were followed for ten years or more, satisfactory results gained the prominence of 85 per cent with only 2.5 per cent of such patients experiencing a clinical relapse. In patients followed for ten or more years it was notable that serologic fastness of the blood to a large extent disappeared.

*Types of Clinical Relapse in Latent Syphilis.* An estimate by the attending physician as to the frequency with which the patient may develop the late and crippling manifestation of syphilis is a problem of first importance to both these individuals. Of the total group of 1,936 patients, there were ninety-four who experience some form of relapse—sixteen had an early infectious relapse, thirty-one syphilitic complications involving the heart and blood vessels, and thirty a central nervous system relapse. In five cases there was visceral involvement, usually of the liver. Of the ninety-four patients who had a clinical relapse, an ultimate satisfactory result was subsequently achieved in twenty of them. In only eight of the thirty relapsed cases with central nervous system involvement was enough damage done to cause distressing manifesta-

tions. In only seven of the thirty-one cases with a relapse involving the heart and blood vessels did the condition develop into an incapacitating one during the period covered. Clinical relapse was found to be only slightly more frequent in patients with persistently positive blood reactions than in patients whose reactions had become negative. The latent syphilitic patient, therefore, is in no special danger because of the persistence of a positive blood reaction. On the other hand, the occurrence of serologic relapse of the blood frequently was demonstrated to be an unfavorable omen. The repeated occurrence of one plus or two plus reactions interspersed with groups of negatives, when the tests were frequently performed, was proven to be an especially unfavorable sign pointing to ultimate complete relapse.

All except three of the patients who had an infectious relapse began treatment in early latency, that is, the disease was of less than four years' duration when the patient reported to the clinic. Three-fourths of the cases having a relapse of any kind received less than twenty doses of arsphenamine in combination with heavy metal. But again it was found that syphilis of the heart and blood vessels was not apparently affected by an increased amount of arsphenamine.

The cooperative clinical group have effectively shown that in latent syphilis the aim of treatment should be the prevention of the development of the late, crippling complications of syphilis. An outline of treatment has been suggested for the latent syphilitic, which consists of twenty-four doses of neoarsphenamine in courses of eight injections alternating with courses of bismuth totaling from fifty to sixty doses. Periods of rest from treatment should be limited to the late latency of syphilis, and in early latency a continuous scheme followed regardless of the serologic response. The subsequent period of observation should be continued during the remainder of the latent syphilitic person's life.

## REACTIONS TO THE ARSENIC COMPOUNDS

The considerable number of records accumulated made it possible to study severe reactions to the arsenicals on a large and more comprehensive scale. Such reactions are of vital importance in the program for the eradication of syphilis. It is a well-known fact that these reactions and the pain associated with intravenous and intramuscular injections cause great aversion to antisyphilitic therapy in some of the less phlegmatic patients, and, indirectly, lapses from treatment. The study of the cooperative clinical group on arsenical reactions included a consideration of 177,360 injections. Among this number two severe reactions and thirteen mild reactions occurred per 1,000 injections. The severe reactions in their order of frequency were icterus, crustaceous dermatitis, ocular damage (found exclusively among 19,964 injections of tryparsamide), purpura hemorrhagica, and in a few instances arsenical stomatitis, aplastic anemia, hepatitis, and encephalitis.

*Difference in Toxicity of Arsenic Compounds.* Every scientist interested in the treatment of syphilis has long desired information relative to the toxicity of the antisyphilitic drugs when applied therapeutically. The many thousand injections given in the clinics of the cooperative group demonstrated that there was some difference in the toxicity of the several arsenic compounds. Arsphenamine ("606") and neoarsphenamine showed an equally low toxicity. Sulpharsphenamine was about 50 per cent more toxic than arsphenamine and neoarsphenamine. Although mild reactions after sulpharsphenamine were less frequent, the number of severe reactions from this drug indicated that it was the cause of much more serious damage than either arsphenamine or neoarsphenamine. Silverarsphenamine was less toxic than arsphenamine and neoarsphenamine but it was also less effective in producing satisfactory end results. Reactions of either a mild or severe type occurred with greatest frequency during the first

course of treatment. Severe reactions, especially crustaceous dermatitis and icterus, were more common among patients in the advanced age groups, while the mild reactions occurred more frequently in the early years of life.

Three-fourths of the patients in whom arsenical treatment was resumed after the first reaction experienced no further difficulty. The best measures found for the prevention of reactions were, in order of success, the postponement of arsenical treatment for at least one month and preferably for from three to six months, changing the variety of the arsenical, and finally lowering the dose.