OBSERVATIONS ON THE TREATMENT OF SYPHILIS

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Syphilis generally is probably as poorly treated as any disease with which we have to contend. Every medical man properly includes syphilis in his field, and should know the modern methods of treatment; unfortunately, many do not. A survey of specific therapy administered to approximately 3,000 civilian syphilitic persons by reputable physicians reveals some rather startling facts. In September, 1919, I¹ reported as follows: Of 113,000 men examined at Camp Travis, 3,000 were found to have infectious lesions of syphilis. A fair proportion of these had consulted reputable physicians at one time or another, and yet we gleaned such facts as the following from their histories: Local caustic and antiseptic applications were freely used by physicians and patients alike, not a single dark field examination having been made in any case prior to entering the service. A negative Wassermann reaction during the first few days of the infection was accepted as sufficient evidence of the absence of syphilis. Late syphilis with negative Wassermann reactions were usually missed. Treatment with pills and mixed treatment were the usual methods employed, but five men having received the equivalent of a single eight-week course of treatment such as outlined by the Surgeon-General's committee on venereal diseases. There seemed to be no plan of treatment other than that directed by the visible manifestations of the disease, and when these disappeared, treatment stopped. The reason why the average doctor believes deep down in his heart that syphilis is an incurable disease is readily understood when his treatment of the disease stands in the light of our present knowledge.

It should be considered criminal deliberately to await the appearance of secondary manifestations of the disease before starting treatment. The so-called tonic treatment should be relegated to antiquity because we now recognize that we are dealing with a constitutional infection that is caused by a specific organism that may be destroyed *in vivo* as well as *in vitro* by definite spirocheticides which in sufficient concentration will destroy every organism encountered. If we were able to stop there, the immediate cure of syphilitic persons would indeed be a simple matter, but unfortunately there are further considerations. We know that the spirochete has a certain affinity for epithelial structures, that it attacks all tissues and organs, and that further, as demon-

1. Guy: Analysis of the Venereal Situation, *Urol. & Cutan. Rev.* **23**:512 (Sept.) 1919.

strated by Nichols,² different strains may determine selective localization of spirochetes difficult to reach with our drugs. Warthin³ describes in minutiae the pathology of syphilis, and states that he has never seen pathologically a cured case of syphilis, but neglects to tell us what treatment cases had had that came to his necropsy table. He shows the facility with which the spirochete localizes in different tissues and perhaps underestimates our ability to destroy the organism. We are limited in our therapeutic attack by the ability of our patients to tolerate drugs, and while toleration varies considerably in different persons, there are certain limits beyond which we dare not go. We estimate dosage of arsphenamin according to the body weight of the person, usually at the rate of 0.1 gm. to each 30 pounds of body weight, because this is well above the amount that is effective from a therapeutic standpoint, and at the same time clinical experience has shown that such an amount may be given with comparative safety. In using mercury we are limited to dosage that will not salivate our patients or damage vital structures, regardless of the salt used or the method of introducing it into the body, and yet we are able to accomplish much with mercury either alone or used in conjunction with arsphenamin.

ARSPHENAMIN AND MERCURY MEDICATION

The relative efficiency of the drugs is in the minds of many an open question. Kolmer's⁴ work in vitro-vivo with arsphenamin and mercury in experimental trypanosomiasis demonstrated trypanocidal action for arsphenamin in a dilution of 1:40,000, and at the same time conclusively demonstrated the superiority of arsphenamin over mercury as a trypanocide. Although we repeatedly examined primary lesions after the injection of a full therapeutic dose of arsphenamin, we were unable to find spirochetes later than one hour and a half after the treatment. When examinations were made at ten minute intervals actively motile spirochetes were first noted, then those with feeble motility, then nonmotile and distorted forms, and finally the absence of organisms. On the other hand, I have on several occasions noted spirochetes seventy-two hours after an injection of mercury. And yet Ehrlich failed in his attempted "therapia magna sterilisans." The principle reason for his failure was the rapid elimination of the drug. Swift and Ellis⁵ were able to find no spirocheticidal activity of

2. Nichols, H. G.: Observations on a Strain of *Spirochaeta Pallida* Isolated from the Nervous System, *J. Exper. M.* **19**:362, 1914.

3. Warthin, A. S.: The New Pathology of Syphilis, *Am. J. Syphilis*, **2**:425 (July) 1918.

4. Kolmer: Chemotherapy of Trypanosomiasis, *J. Infect. Dis.* **20**:10, 35 (Jan.) 1917.

5. Swift and Ellis: *New York M. J.* **96**:53, 1912.

blood serum six hours after the injection of a full therapeutic dose of arsphenamin. Another reason for Ehrlich's failure is the facility with which the spirochete buries itself far from the general circulation.

In order to overcome these difficulties Pollitzer⁶ states that "salvarsan should be administered in sufficient dosage, repeated at such intervals that the blood is kept charged with the drug for several days continuously." He approaches these conditions by giving arsphenamin on each of three successive days at the rate of 0.1 gm. to each 30 pounds of body weight, followed by a course of mercury. By this method he has been able to bring about a reversal of the Wassermann reaction in cases in which it has been persistently positive after repeated courses of less intensive medication. He also reports a series of patients with primary syphilis—in which the diagnosis was made by the dark field method, the Wassermann reaction being negative—in which a single such course was given. After about a year there was no indication either clinical or serologic of syphilitic infection. I have treated twenty-five patients in a similar condition in the same manner, and have kept ten of them under observation for a year without being able to demonstrate clinical or serologic evidence of remaining infection. In ten other patients with primary syphilis, three of whom already had positive Wassermann reactions, I have used a modification of his plan. As soon as the diagnosis was established, arsphenamin at the rate of 0.1 gm. to each 30 pounds of body weight was given on each of three successive days; two weeks later this treatment was repeated; and in a month three more injections were given, making a total of nine injections in six weeks. With this, weekly injections of the mercuric salicylate were given for a total of ten weeks, making a total of nine injections of arsphenamin and ten of mercury in ten weeks. Six of these patients were under observation for a year with negative results; the other patients were lost by transfer to other camps or overseas. The balance of our primary cases, numbering about 365, were given routine treatment according to the plan of the Surgeon-General's advisory committee. These patients were given two complete courses, each comprising eight injections of arsphenamin and eight of mercury, the therapeutic rest period being five weeks. We have been unable to keep many under observation for a year, but the majority of them were clinically and serologically negative when last examined. About a third of the patients were under observation for at least eight months. One developed an annular macular eruption and four others were found to have positive Wassermann reactions within this time. In young, robust persons with pri-

6. Pollitzer, S.: *The Principles of the Treatment of Syphilis*, J. Cutan. Dis. **24**:633 (Sept.) 1916.

mary lesions our aim is to abort the disease by destroying every infecting spirochete, and this may be done with a reasonable degree of certainty when we overcome the obstacles to Ehrlich's hoped for immediate therapeutic victory.

LENGTH OF TREATMENT AND DOSAGE

There are two ways in which we may expect to destroy more spirochetes in a given length of time; one is by giving arsphenamin at more frequent intervals, and the other is by increasing the amount administered at each injection. I have repeatedly given arsphenamin at the rate of 0.1 gm. to 20 pounds of body weight, up to and including 0.8 gm., without reaction. In one patient weighing 120 pounds, 0.5 gm. was given on each of three successive days without untoward results. With manufacturers offering a drug of much lower toxicity than formerly it seems logical to take advantage of the opportunity to increase our therapeutic results. A plan to keep the blood stream saturated with arsenic for a considerable number of hours that is worthy of mention is that of Reiger.⁷ He uses neo-arsphenamin, on account of the low toxicity, giving 0.9 gm. at the first injection, 0.6 gm. in an hour and 0.3 gm. at the end of the third hour. The time and amount of the injections are based on the elimination rate of the drug. Much better clinical results are claimed by this than by ordinary methods. The theory is advanced that arsenic will reach the spinal fluid in appreciable amounts after such treatment.

Fordyce⁸ believes that in routine work, injections should not be given at shorter intervals than from five days to a week, and in this respect most syphilographers are in accord, favoring rather a method of fractional sterilization than to attempt an immediate therapeutic victory. Short, intensive courses of arsphenamin and mercury used in conjunction are favored. Such methods have the advantage of comparative safety over more intensive treatment, and certainly no one can discount the results that have been obtained. The length of courses varies in different hands, but usually comprises from eight to ten weekly injections of arsphenamin and the same number of injections of mercury, followed by a period during which no medication is given. The necessity of rest periods during antisyphilitic treatment was long ago pointed out by Fournier. In the laboratory, Noguchi⁹ has been

7. Reiger, J. B., and Solomon, H. C.: The Circulation of Arsenic in the Cerebrospinal Fluid, *J. A. M. A.* **71**:15 (July) 1918.

8. Fordyce, J. A.: Diagnosis and Treatment of Syphilis, *Am. J. Med. Sc.* **152**:469 (Oct.) 1916.

9. Akatsu Seinai and Noguchi Hideyo: The Drug Fastness of Spirochetes to Arsenic Mercurial and Iodide Compounds in Vitro, *J. Exper. Med.* **25**:349 (March) 1917.

able to increase the tolerance of spirochetes for arsphenamin five to six fold by gradually increasing the amount of the drug in his culture medium. The toleration for mercury was increased from thirty-five to seventy times the original. He also found that this acquired immunity on the part of the spirochete to the action of arsphenamin and mercury would disappear on cultivation in mediums free of the drug. Thus Noguchi produced scientific proof of the accuracy of Fournier's clinical observations and placed on a scientific basis the prolonged intermittent treatment of syphilis. The patient should be given a rest period of sufficient length to recover physically from the course of treatment just finished, as well as to prevent the formation of an arsenic and mercury fast strain of spirochete from too sustained treatment, the time being limited by the probable date of clinical or serological recurrence. I consider that a period varying from five to eight weeks is required. At the close of a rest period a Wassermann reaction will be obtained that will give a more reliable check on the results of therapy than that which might be taken while the patient is on active medication.

DEPENDENCE OF TREATMENT ON INDIVIDUAL AND ON STAGE OF DISEASE

Regardless of theories and plans for the treatment of syphilis, however, we must remember that we are treating a patient as well as a disease, and govern ourselves accordingly. Absolute generalization in the application of specific therapy will lead to disaster. All patients may not be treated intensively. Some will not tolerate mercury in one form or another, and there are some who cannot tolerate arsenic. One must be very cautious in the application of antisyphilitic treatment, particularly with pathologic conditions affecting the cardiovascular, renal and pulmonary apparatus, and with modifications of therapy as the result of such pathology, one must necessarily continue treatment much longer. Again, the kind and amount of treatment will vary with the stage and location of the disease. One is justified in disregarding the possibility of reaction following arsphenamin in order that treatment may be started twenty-four hours sooner in cases of dark field positive cases than would otherwise be possible. It is obvious that a patient with a primary lesion will require less treatment than one with florid manifestations of an early generalized infection; he, in turn, will require less treatment than a patient with a long standing infection, and the patient with evident infection of the central nervous system will require more treatment, and in many cases the application of special therapy, to reach the disease. The chances of a cure are to some extent dependent on not only the kind of treatment that the patient receives, but also on the status of the infection at the time

treatment is instituted. Our ideas as to the amount of treatment necessary to cure syphilis are largely empiric, but we no longer blindly state that from three to five years of mercurial treatment are necessary to cure any case of syphilis. The advent of arsphenamin has materially shortened the time, as has also early diagnosis by the dark field method and correspondingly early institution of vigorous specific treatment. In the Wassermann reaction we have an invaluable aid in determining the effect of therapy, but in order that we may arrive at any definite conclusions bearing on the question, we must take into consideration the opinions of close observers with vast experience in modern therapy. Fordyce⁸ states that in primary syphilis, before the Wassermann reaction has become positive, it is possible to abort the infection; that such patients should receive two courses of arsphenamin and mercury used in conjunction; that in secondary syphilis three courses is usually the minimum required; while in tertiary cases the method of treatment depends on the tissues or organs involved. Using weekly injections of arsphenamin and an insoluble salt of mercury in six-, eight- and ten-week courses, we consider that one course will cure a certain percentage of cases, but that two courses are usually needed. Pollitzer shows that one course such as he advocates will cure, but gives his patients an additional course of the same kind "for insurance." Of patients with secondary manifestations at the time of the beginning treatment, I require a negative Wassermann reaction and negative clinical findings after each of three consecutive courses of treatment. This has often meant four, five or six courses instead of three, but I believe it is necessary, because when the patient becomes asymptomatic, our principal guide is the Wassermann reaction, and failure to cause its reversal after a course, or a return to positive after the reaction has been negative spells an active infection.

Of about 2,500 patients with early or secondary syphilis, comparatively few were held in camp sufficiently long to complete three courses of treatment; many of them were sent to France after a single course of treatment if the Wassermann reaction was negative, and they were free from lesions, treatment being continued on their syphilitic registers regardless of where they were sent. It is interesting to note that eight weekly arsphenamin and a similar number of mercury injections caused a reversal of the Wassermann reaction in over 98 per cent. of these cases. Approximately 1,000 men received two courses and about 300 were given three courses, a few patients with refractory cases receiving additional courses according to the indications. None of these patients had been under observation sufficiently long to justify any conclusions regarding the end results of the therapy. As a rule, the older the infection the most difficult it is to cure. In late cases, repeated courses plus the iodids, for their effects as resolvents of

specific infiltrations, are necessary. When we have given the treatment we believe to be indicated, and have obtained repeated negative Wassermann reactions in addition to a clinical cure, we stop all treatment, keeping the patients under observation for at least a year during which the Wassermann tests are made every two or three months. With negative clinical and serologic findings at the close of the year of observation, it is customary to give a provocative injection of arsphenamin and to repeat the Wassermann test. As to the value of the provocative treatment, physicians do not agree. We know that the antibody content of the syphilitic blood may vary from time to time to such an extent that at one time the reaction may be weakly positive and the next time frankly negative. In an attempt to obtain some information on the subject we have in some cases used the provocative injection and in others merely repeated the Wassermann test at intervals. The number of cases available for this comparison was unfortunately too small to be conclusive, but we were not able to demonstrate provocative properties for small injections of arsphenamin. It is our impression that two- or three-week courses of iodids at times produce positive Wassermann reactions in clinical syphilis with negative tests. We have no definite data to offer in support of this theory; it is a clinical impression only, as far as we are concerned. We have used the method many times and apparently in a fair percentage of our few cases with provocative results, but the same objection holds in these cases that does in the case of the provocative injection of arsphenamin.

INTRASPINAL THERAPY

Before any patient with syphilis is finally discharged a lumbar puncture is made to determine the presence or absence of infection in the central nervous system. If there is any indication of neurologic involvement before this time, of course, we do not wait, but when we realize that most of our central nervous system infections are cured by the treatment usually applied, as evidenced by the discrepancy between the number of cases showing early positive spinal findings and the infrequency of positive findings after ordinary treatment, certainly routine treatment should be given a thorough trial before special therapy is resorted to. A small group of patients with infections not more than six months old were punctured in my service and positive findings noted in 10 per cent., as evidenced by a cell count of over five, an increased globulin and a positive Wassermann test or certain changes in Lang's gold test. These patients were put on routine treatment and after two complete courses were again punctured, and only one case was doubtfully positive. It is interesting also to note that one-half of the cases with persistently positive Wassermann reactions after two courses of treatment had positive spinal fluid findings. Fordyce⁸

reports positive spinal findings in 20 per cent. of one series of secondary syphilis and 25 per cent. in another, and says it is his belief that the spirochetes are destroyed spontaneously or by therapeutic agents administered in the usual way. Obviously, early intensive treatment will prevent most late neurologic complications. The older the infection the greater the likelihood of such involvement and the more difficult its eradication.

In patients with persistent inflammatory changes in the spinal fluid additional intensive intravenous medication may bring about the desired result, or intraspinal therapy, or a combination of the two may have to be used. The same general principles hold in the sterilization of a focus of infection in the central nervous system as in the general treatment of the disease, but a modified method of therapeutic attack is necessary on account of the anatomy of the part. Direct saturation of the spinal fluid with comparatively large amounts of arsphenamin or mercury is impracticable on account of the irritating effect, and in some cases fatalities, due to overdosage. The original technic of Swift and Ellis¹⁰ or the modification of Ogilvie,¹¹ with the direct addition of arsphenamin to blood serum, are the methods most in vogue at the present time. Dosage is begun with minimum amounts and gradually increased if well tolerated, about 0.5 mg. being considered the limit of safety. Treatments are given in courses, the intervals between them varying according to the reaction after each injection. Much has been said from a theoretical standpoint against intraspinal therapy, but no amount of scientific discussion can discount results that have been obtained when the method has been properly used. Speaking from a prognostic standpoint, Fordyce¹² says: "When symptoms are due to an active inflammation with strongly positive fluid, the outlook is very encouraging. Where, however, the underlying process is one of degeneration with atrophy and sclerosis, with negative or weakly positive fluid findings, the prognosis is not so hopeful."

There are those who condemn the method unreservedly, and there are those who are accused of being overenthusiastic, and according to their faith, the indications vary in the minds of different men. I should be inclined to exhaust intensive general medication before resorting to intraspinal therapy, and having done so, I should expect some clinical results in cases in which the pathologic process was not too far advanced.

10. Swift, H. F., and Ellis, A. W. M.: The Treatment of Syphilitic Affections of the Central Nervous System with Especial Reference to the Use of Intraspinal Injections, *Arch. Int. Med.* **12**:331 (Sept.) 1913.

11. Ogilvie: *J. A. M. A.*, 1914, No. 63.

12. Fordyce, J. A.: Syphilis of the Nervous System, *J. Cutan. Dis.* **34**: 713 (Oct.) 1916.