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THE SIGNIFICANCE OF A POSITIVE BLOOD TEST FOR SYPHILIS

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In the campaign against syphilis recently initiated by Surgeon General Parran of the United States Public Health Service, blood tests will play a dominant role in detecting the disease and in estimating the effects of treatment. It is, therefore, important that the results of these tests, particularly the positive reaction, be correctly interpreted. The thirty years which have passed since the invention of the Wassermann test have seen many changes and additions to methods of performing blood tests for syphilis. During this time, the correlation of clinical data with information on the blood reaction of both syphilitic and non-syphilitic patients has caused us to modify some of our ideas about the meaning of a positive blood test for syphilis.

General Considerations

1. Flocculation tests are, generally speaking, more efficient than Wassermann tests:- Before discussing the significance of a positive blood test for syphilis, it is well to call attention to a rather general but false belief that a Wassermann test or any of its modifications is more reliable than a flocculation test, of which the Meinicke, Kahn, Kline, Hinton and Eagle tests are some examples. In theory, these two types of tests are based on the same principles; the essential difference is in the technique of their execution. In actual practice, as shown by surveys of the League of Nations and of the United States Public Health Service in co-operation with the American Society of Clinical Pathologists, the flocculation tests are, in general, more accurate than the Wassermann. A recent

editorial in the American Journal of Clinical Pathology sums up the situation in these words, "On the basis of both sensitivity and specificity, the flocculation tests are equal or superior to the complement fixation tests."[1] Besides this the flocculation tests have, in my opinion, definite practical advantages. In the first place, they are simpler and therefore more likely to be performed in the manner recommended by their inventors; and secondly, since they require fewer variable reagents, they should, if devised so that they are easy to do and easy to read, give practically the same results in all laboratories that perform them carefully.

2. Accuracy of individual laboratory is important.

In judging the significance of a positive blood test, it is necessary to consider not only the efficiency of the method but also the accuracy of the laboratory employing it. This is strikingly exhibited in a recent report of the Committee on the Evaluation of Serodiagnostic Tests for Syphilis.[2] According to this report, when fifteen different laboratories using one much-used complement fixation method carried out tests on specimens from a group of 200 persons known to have syphilis, the number of positive tests reported by the separate laboratories varied from a minimum of 31.8% to a maximum of 71.4%. On specimens from presumably non-syphilitic cases which might be expected to yield only negative tests, there was also disagreement, for although some of the laboratories reported no false positive tests, two of the fifteen submitted 3% of false positive reactions on identical specimens of blood. Another group of thirteen laboratories using a well-known flocculation test on comparable specimens obtained results varying from 37.6% in one laboratory to 83.7% in another; and two of the laboratories in this same group reported as

many as 2% of false positives on serum from presumably normal persons. Such differences in reports between separate laboratories using the same method make the significance of a positive reaction extremely dubious unless the accuracy of the laboratory making the test is known. It is to be hoped that this difficulty may be overcome by some system of certification indicating the degree of accuracy with which a laboratory performs any given test for syphilis.

Significance of Positive Tests in Relation to Diagnosis

Under this heading, I shall discuss only the value of blood tests in determining the existence of syphilis, deferring until later the consideration of their value as an indication for treatment.

1. Positive blood test accompanied by history or clinical signs of syphilis:- In patients who have a history or signs of syphilis, a positive blood test is ordinarily all that is required for an accurate diagnosis, but even here caution is needed to exclude a false diagnosis on the basis of a single positive blood test. The following will illustrate this: An ulcer on the penis was incorrectly diagnosed as a primary lesion because of an accompanying positive blood test. In the opinion of another physician, however, the ulcer was clinically not a primary lesion; repeated darkfield examinations showed no treponemes; treatment was withheld; blood tests and darkfield tests were continued; the patient's serologic reaction became negative in a few weeks; he never developed signs of secondary syphilis, and it was concluded that he did not have syphilis. In another case, a competent dermatologist diagnosed a rash as that of secondary syphilis on the basis of a single positive blood test. Subsequent blood tests were negative, and the course of the disease showed it to be a case of psoriasis. Although such mistakes as these

are perhaps uncommon, their occurrence is increased by placing complete faith in a positive blood test as indisputable evidence of syphilis. Therefore, inasmuch as there are signs or symptoms which may simulate those of primary or secondary syphilis, more than a single positive blood test should be had if there is any doubt about the diagnosis.

Since tertiary syphilis is not directly communicable four to five years after infection except by a mother to her offspring, it is seldom necessary from the standpoint of public health that treatment for these patients be started immediately. Therefore, before a diagnosis is made or treatment is started, a positive blood test in a person with suggestive symptoms of tertiary syphilis should always be confirmed by a repeat specimen; besides this, it is always wise to seek all other possible evidence on the certainty of infection. This may often be obtained by examining a husband's, wife's, or mother's blood and by a careful history concerning past exposures. Such caution in the interpretation of a positive blood test is not advised to minimize its significance, but to emphasize the importance of clinical evidence in a diagnosis of syphilis. In fact, since repeatedly positive blood tests by the more accurate methods usually do indicate syphilis, the physician should in all doubtful cases exclude or confirm this disease by a most careful investigation. This is equally true if there is a negative Wassermann and Kahn, but a positive Hinton test. A persistently positive Hinton is, in my opinion, almost as much evidence of syphilis as if all of the tests were positive.

From the foregoing, it must be apparent that an accurate diagnosis of syphilis in any stage can be made only when it is based on clinical evidence plus the positive blood test.

2. Positive blood test unaccompanied by history or clinical signs of syphilis:- Although the most common and most important evidence of infection with syphilis is a positive blood test, this reaction may also be caused by other diseases: yaws, as commonly as syphilis; leprosy, in from 40% to 60% of the cases; sometimes tuberculosis or cancer; and occasionally other diseases. It may, for that matter, be obtained as the result of errors in laboratory technique or, rarely, because of imperfections in even the best blood tests. Indeed, in the recent evaluation of laboratory tests for syphilis this point was strikingly brought out by the committee in charge of the evaluation.[3] I quote their opinion, "The committee found no justification for a diagnosis of syphilis in a number of cases, particularly in one series in which the diagnosis had been based on a single false positive reaction." The committee recommended that if a positive blood test is obtained in a person with no history or clinical evidence of syphilis, the test should be repeated in the same laboratory, using two or more different methods. Even such a procedure as this is not conclusive evidence of the existence or non-existence of syphilis. For example, in one of the evaluation studies, 10 of the 13 different tests for syphilis on a single patient were positive, yet it was concluded on exhaustive clinical evidence that the patient was not syphilitic, but tuberculous.[4] Consequently, one sees the fallacy in the all too prevalent belief that the result of a laboratory test alone may safely be used to diagnose syphilis.

For reasons such as these, I believe that when no clinical

evidences of the disease exist, a positive blood test is the signal, not to begin treatment forthwith, but rather to confirm the positive reaction by repeated serologic examinations, and then to study the patient -- his history, his family, his spinal fluid -- to determine whether or not he really has syphilis. For this purpose, a consulting syphilologist is recommended. The better hospitals meet the problem by referring the patient to one of its physicians who specializes in syphilis. Such a physician has acquired the knack of eliciting a history or "collateral evidence", as Stokes calls it, bearing on syphilis. He is often able to elicit information that not only warrants a diagnosis of this disease, but indicates the approximate time of infection. This latter knowledge is a most important factor in the management of syphilis, because the duration of infection in a person not only defines his capacity to transmit the disease, but also suggests the likelihood of later injuries.

If clinical evidence is so necessary for an accurate diagnosis of syphilis as has been indicated, it may well be asked, "What is the good of doing blood tests?" This partial list of reasons is sufficient answer: positive blood tests (1) abundantly verify clinical syphilis; (2) usually give doubtful clinical evidence real significance in diagnosing syphilis; and (3) which is perhaps most important, detect fully 50% of syphilitics who would not otherwise be suspected.

Significance of Positive Blood Tests in Relation to Prognosis

No blood test, in itself, defines the outcome of syphilis:- Some laboratories report [illegible] the intensity of the reaction that occurs when the patient's serum and the reagents of

the test are mixed. Whether such a quantitative evaluation of a positive blood test is made by using more than one dilution of serum, as in the Kahn test, or by visual estimation of the strength of the reaction in one test-tube, it is valuable chiefly in providing the laboratory with a check on itself and is of no value in the management of syphilis. My reasons for believing this are briefly as follows: the strong reaction, commonly designated as a 4-plus test, may be found in all stages of syphilis and is quite as apt to occur in those who are readily amenable to treatment as in those who resist it to the extreme. On the other hand the weak, or the so-called 1-plus, test may likewise be found in every stage of syphilis, although rarely in the second stage. It may be found in persons who are fatally injured by syphilis as well as in those who give no manifestations of it. In short, the strength of the reaction throws no light on the stage of the disease, nor on the character, duration and the site of the lesions; these are the factors, all of them clinical, upon which we actually base our prognosis. This conception of the relative unimportance of the strength of a positive reaction in prognosis is difficult to acquire, because in the test tube the strongly positive reaction is striking. The words "strongly positive" are equally striking and carry the implication of "bad" syphilis as contrasted with the "mild" syphilis implied by the report of a weakly positive test. Such inaccurate conceptions concerning the significance of a positive blood test are unfortunate, and can easily be avoided if the results are reported simply as positive, negative, or doubtful.

Significance of Positive Blood Tests in Relation to Treatment

Although a positive blood test, in most cases, is good

evidence that syphilis exists or has existed, it sheds no more light on the necessity for treatment than a positive tuberculin test does in tuberculosis. It would be fine if syphilis could be adequately managed purely on the results of blood tests, or even largely so. Then a positive laboratory report would call for treatment, and if the report were negative, no treatment would be given. As is well-known, the successful treatment of syphilis is far more complex than this and is actually based largely on clinical knowledge of the course of the disease. If the clinical picture indicates that the patient is infectious or that he is likely to receive further injury from the disease, or that he has tertiary injuries which need to be healed in hope of restoring the injured tissue to normal function, the positive blood test merely aids in establishing syphilis as the etiology. The criteria by which treatment is administered, however, is based on the stage of the disease and its manifestations. This is shown by the fact that there are plans of treatment recommended for the early stages of the disease, and that there are other pretty definite schemes of treatment for such tertiary manifestations as cardio-vascular syphilis, neuro-syphilis and hepatic and other forms of visceral syphilis.

Most syphilologists recommend that all patients who have repeatedly positive blood tests, even if there is no other evidence of syphilis, be treated for the disease, provided there are no contra-indications because of age or physical condition. However, I believe that a positive blood test, unsupported by any other clinical finding, is not an indication for immediate treatment but for a thorough investigation designed first of all to establish that the patient has syphilis, and secondly to throw some light on the duration

of the infection. If in the opinion of a skilled syphilologist there is absolutely no clinical evidence of the disease, I recommend an examination of the heart and aorta by a cardiologist and an x-ray expert, and an examination of the spinal fluid. If the spinal fluid and other examinations disclose no evidence of syphilitic injury, I recommend that blood tests be made at monthly intervals for at least a year, and the spinal fluid again examined. If it is still negative after this year of observation, I do not believe that the positive blood tests should be a sign to begin treatment, unless the individual is a pregnant woman or is contemplating early marriage.

My reason for recommending a long period of observation rather than treatment for those with repeatedly positive blood tests as the sole evidence of syphilis is based on a consideration of the groups into which these cases appear to fall. If, for example, the clinical evidence seems to favor congenital syphilis, a decision to treat or not to treat should depend largely upon the patient's age. It rarely happens that congenital syphilitics who reach the age of 21 and have positive blood tests but no other sign of the disease are injured by it in later life. The tabulations of Jeans & Cooke indicate that after the age of 19 the chances of late injury are one in one hundred and ninety-three,[5] and the tabulations of the American Clinical Co-operative Group appear to extend this likelihood for interstitial keratitis up to 25 years of age.[6] If the clinical evidence -- exposure, etc. -- is more consistent with acquired syphilis, and the circumstances of the patient's life suggest that he has been infected more than twenty years, the physician who is influenced by Brusgaard's observations[7] would feel that later injury is very improbable. In such cases, most syphilologists handle the

problem of treatment on the basis of the patient's age by saying that persons beyond 50 who have a positive blood test and no other signs of syphilis do not require anti-syphilitic treatment that includes arsphenamine. Indeed, some physicians doubt the wisdom of treating these patients at all.

Next, may any dependable inferences be drawn from the disappearance of a positive test or decrease in the strength of the reaction during treatment, and from a fixed or a resistant positive reaction? The answer is, practically speaking, no. For if treatment is withdrawn simultaneously with the disappearance of the positive reaction in early syphilis, it will in most instances have been withdrawn far too early; and if it is continued on the basis of a fixed or a resistant reaction in late tertiary syphilis, it will in many cases be continued far too long. In the present state of our knowledge concerning the serology of syphilis, the treatment of fixed positive blood tests is a dark page. One almost shudders to see a congenital syphilitic treated for five, ten, fifteen or even twenty years almost continuously, merely on the basis of a positive blood. The persisting positive has no prognostic significance. Many syphilologists recognize this by saying that those patients with fixed positive reactions fare no worse than do those who become negative, an opinion definitely verified by the statistics of the American Co-Operative Clinical Group.[8]

In one important regard, blood tests repeated at approximately two-month intervals are of the greatest advantage as a guide in treatment; this is during the early stage of syphilis, when a relapsing positive is a warning that treatment is not controlling the disease. I say this because the studies of the American Co-Operative Clinical

Group as well as our own show that in about half the cases of early syphilis in which there was a relapsing positive, there was also a clinical outburst of the disease. The significance of a relapsing positive in patients infected from five to twenty years is not so clearcut; nevertheless, I would personally be inclined to pay a great deal of attention to it during the first ten years of the disease, and decreasing attention to it during the next ten years. In patients infected more than twenty years, serologic relapses do occur, but I ascribe no especial significance to them, for they are not uncommon and, as far as I know, are practically never followed by clinical manifestations of active syphilis.

I shall sum up this brief sketch concerning the significance of a positive blood test by saying: (1) that an accurate flocculation test for syphilis, competently done, offers the best aid in detecting the disease; (2) that the strength of a positive reaction is without significance in prognosis; (3) that a positive blood test is perhaps the most valuable aid in the diagnosis of syphilis, but by itself is not diagnostic; and (4) that a positive blood test alone is not a sign to begin treatment nor, if it persists, a sign to continue it.

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