

## Medical Progress.

### PROGRESS IN DERMATOLOGY.

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#### THE SERUM DIAGNOSIS OF SYPHILIS.

(Concluded from No. 15, p. 477.)

*Experiments upon apes.*—Much valuable information in regard to the reaction was obtained by experiments upon apes which were chiefly carried on in Batavia.<sup>8</sup> The results were confirmed later by clinical experiments upon men. Among other facts these animal experiments demonstrated that apes whose serum was free before infection developed antibodies after infection and that in the lower apes, in whose serum syphilitic antibodies were sometimes present under normal conditions, although in small amount, infection brought about a marked increase in the amount of these antibodies. It was found, however, that the injections of living or dead syphilitic material could cause an increase of the antibodies only up to a certain point. It was also demonstrated that the antibodies disappeared rapidly after the cessation of the injections. Occasionally antibodies were found in the serum before the appearance of the primary lesion. This was considered to be indicative of an early saturation of the organism. In some cases antibodies were found as early as on the seventh day after the infection. Moreover, these experiments upon apes convinced the writers that the serum reaction was specific in syphilis.<sup>9</sup>

*Clinical results.*—Wassermann estimated<sup>20</sup> that up to December, 1907, his method had been used in over 1,000 cases. The number of investigators who have reported their results is not very large, however. Blaschko<sup>5</sup> reports 270 cases, the larger proportion of which gave positive reactions, whereas all of his non-syphilitic cases were negative. Blumenthal and Wile<sup>6</sup> report 50 cases in which both serum and urine were tested at the same time. Forty-one of these cases were undoubtedly syphilitic. They found the reaction positive in both serum and urine in 41 cases, negative in both in 6 cases and positive in the serum but negative in the urine in 3 cases. Stern,<sup>8</sup> collaborating with Bruck, tested 378 cases of treated and untreated syphilis and obtained a positive reaction in 53%. On the other hand, of 157 non-syphilitic cases, only 2 gave suspicious reactions. Citron<sup>9</sup> found the reaction positive in 74% of his cases of undoubted syphilis, while not one non-syphilitic case reacted. Hoffmann and Blumenthal<sup>18</sup> report a positive result in 80 cases out of 100 in all stages. Meier<sup>18</sup> tested 314 sera, 181 of which were from patients who either gave a history of syphilis or showed the disease clinically at the time of the test. Of the 181 syphilitic sera 81.7% were positive, 2.7% questionable and 15.6% negative. Twenty-one non-syphilitic sera were all negative. Michaelis<sup>19</sup> got 9 positive reactions in 12 cases of undoubted syphilis, mostly late forms, one weak reaction and 2 negative. Of 26 cases without demonstrable

syphilis 2 gave positive reactions, 1 weak, 23 negative. He also obtained one positive reaction with normal rabbit serum. A moribund case of typhoid which reacted strongly to the Widal test was also positive to the syphilitic test, but in two other typhoids the reactions were negative. Schutze<sup>24</sup> reports 12 cases of tabes, 8 of which were diagnosed as syphilitic and 4 as non-syphilitic. The 8 syphilitic cases all reacted positively, the 4 non-syphilitic all negatively. The controls were all negative.

*Results with normal extracts.*—From these results obtained in nearly 1,300 cases it is shown that about 80% of the undoubted syphilitics gave positive reactions to the syphilitic extract (antigen), about 20% a negative reaction and that a positive reaction occurred only exceptionally in non-syphilitic cases. When, however, in the course of extended investigations, non-syphilitic extracts (antigen) were substituted for the syphilitic, it was discovered that they gave results about equal to those obtained with a syphilitic antigen. The claim made by Braun<sup>7</sup> and Weil and Braun<sup>32</sup> that the Wassermann method would give positive results with extracts of normal liver was confirmed by Citron,<sup>9</sup> Landsteiner,<sup>14</sup> Levaditi and Marie<sup>17</sup> and Michaelis.<sup>19</sup> Moreover, Michaelis and Citron both obtained positive results with extracts of the liver of a case dying of carcinoma of other organs. In judging of these results the exceedingly important fact is to be noted that the normal extracts (antigen) gave positive reactions with syphilitic sera (antibodies) only. Weil and Braun,<sup>32</sup> who are strongly opposed to the Wassermann method, admit that "the extract of normal liver gives a reaction only with such fluids as show complement fixation with syphilitic extracts also."<sup>32</sup> Citron<sup>9</sup> states that "the reaction obtained with normal liver extracts showed very marked parallelism with the reaction obtained with syphilitic livers but which, nevertheless, manifested certain small differences which were sufficiently well marked to distinguish it from the syphilitic reaction. I could nearly always predict from its behavior with the normal liver extract which case would react positively to the syphilitic liver." Wassermann now admits the correctness of these results.

*Post-mortem results.*—Besides these clinical experiments just recorded we have reports from Blaschko, Lesser and Pick of post-mortem experiments with serodiagnosis. Lesser states<sup>10</sup> that for years he has been convinced by his autopsy records that syphilis of the internal organs is rarely recognized clinically. His results with the serodiagnostic method have now confirmed his earlier results. Accepting as correct the current estimates of the prevalence of syphilis in Berlin as 20% of the population, he found that of all patients over twenty-five years old coming to autopsy it was possible to demonstrate in about 9%, or about one half of the syphilitics, some form of late syphilis of the internal organs which also had in most cases not been recognized clinically. As Lesser and Michaelis obtained at autopsy a positive reaction in about 52% of those

cases infected several years before and showing no symptoms, Lesser concludes that the serum reaction is positive in about the same proportion of cases as autopsy shows to be syphilitic with absence of clinical signs. Blaschko<sup>5</sup> concludes from the results of over 8,000 autopsies that more than one third of the patients who have had previous syphilis succumb to their present infection. Therefore he considers the agreement which Lesser found existed between the anatomical signs of syphilis and the results of the serum reaction as striking. Pick and Proskauer<sup>21</sup> studied the results with the serum reaction of blood obtained within twenty-four hours after death by aspiration of the right heart or of a large vein. They believe that the results show that the serodiagnosis will render sharper post-mortem diagnoses possible.

*Effect of treatment.* — A study of the effect of treatment upon the reaction is important because of its relation both to the failure of the reaction in some cases of syphilis and also to the prognosis. Opinions vary considerably as to the influence of treatment upon the reaction. Blaschko<sup>5</sup> found that even Fournier's method of the continuance of treatment for ten years did not prevent a positive reaction in every instance. On the other hand, he observed cases in which the reaction, positive before treatment, became negative after treatment. Bruck<sup>8</sup> obtained only 1 positive reaction from 14 apes previously treated with mercury. Out of 10 apes treated with atoxyl, 9 reactions were negative; of 8 treated with iodine, 5 were negative; of 8 treated with arsenious acid, 4 were negative. Stern<sup>8</sup> believed that treatment exercised great influence, for he found syphilitic antibodies in only 29.5% of the treated cases, compared to 82.3% in the untreated. He concludes that treatment kills or at least weakens the syphilitic virus. Citron<sup>9</sup> seems to believe with Blaschko that while mercury does influence the syphilitic virus so that antibodies are no longer produced, the effect is only temporary, as the antibody curve shows a rise before every relapse. Citron states that the earlier mercurial treatment is instituted, the longer it is continued, the oftener it is repeated and the shorter the time since the last "cure," the smaller the antibody content and the oftener it is nil. Lesser,<sup>16</sup> Meier<sup>18</sup> and Michaelis<sup>19</sup> all agree that mercury will cause the reaction to become negative, while Hoffmann and Blumenthal<sup>13</sup> are doubtful. Meier<sup>18</sup> does not think that the effect of treatment is very lasting as "in cases of less than one year since the last symptoms, and all of which had had energetic treatment during the active period, nearly all showed the presence of antibodies, and the majority in abundance." Lesser agrees with Blaschko that mercury does not prevent the return of the antibodies. While, therefore, Bruck and Stern<sup>8</sup> would accept the amount of antibody present as a guide to the efficiency of the treatment, the majority of the writers will say no more than that a negative reaction after treatment is encouraging.

*Value of positive reaction as indication for treatment.* — In regard to a positive reaction as an indication for treatment, the only question which can

arise as to its value is in connection with old cases which have had no recent symptoms. So long as we remain ignorant of the inner meaning of the reaction this question cannot be answered definitely, and therefore most writers express their opinions very cautiously. To quote Hoffmann and Blumenthal,<sup>13</sup> "Where the reaction is positive in late cases which have previously undergone satisfactory treatment, and which have shown no symptoms for a long time, we should be on the watch for a return of symptoms, but unless clinically demanded we should not necessarily advise a renewal of treatment." Blaschko<sup>5</sup> says that in such cases with a positive reaction we may institute treatment in the hope of making the reaction negative. He continues, "But what then? Shall we keep on repeating the treatment forever?"

*Clinical value.* — From what has gone before, therefore, we may conclude that the Wassermann reaction is not specific in the strict meaning of the word, and also that its exact value as an indication for treatment cannot be given until the question of the nature of the reaction has been solved. Nevertheless, if we are careful to separate the fact of the reaction from the theory, the results which we have quoted seem to justify the conclusion that the reaction may have a certain clinical value. As stated by Hoffmann and Blumenthal,<sup>13</sup> "However interesting the theory may be, the main question is whether the fact has been sufficiently demonstrated to give it clinical value." The discussion of the subject of the serum reaction at the XIV International Congress represented the prevailing German opinion as follows: "The reaction is not specific for syphilis since in many instances it also gives positive reactions with normal material. On the other hand, its diagnostic usefulness is not destroyed thereby, as, up to date, such reactions have been met with only in connection with syphilitic sera."<sup>35</sup> At a recent meeting of the French Dermatological Society, however, the members were inclined to doubt if the serodiagnosis possessed any clinical value in syphilis.<sup>36</sup>

*Prognostic value.* — Because of our ignorance in regard to the real nature of the reaction, the prevailing opinion is that, as in all biological tests, a negative result means nothing, while it is by no means proved that in every case a positive reaction means the existence of an active syphilitic process. Wassermann, as has already been mentioned, will merely say that a positive reaction indicates syphilis at some time either past or present.<sup>30</sup> That a positive reaction does not always mean a clinically active process is well illustrated by Citron's case<sup>9</sup> in which the reaction was positive although there had been no clinical symptoms for years, and also by Hoffmann and Blumenthal's case.<sup>13</sup> The latter reported a positive reaction in a man "who had been infected thirteen years before, had undergone a thorough mercurial treatment and had been free from all symptoms for twelve years. Eight years ago he married and his wife and children have remained entirely free from the disease." On the other hand, that the reaction may have some prognostic value is shown by such results as Bruck and Stern<sup>8</sup> report, in

which the results of the serodiagnosis were confirmed later by clinical observation.

*Development of theory.* — A brief review of the development of the theory will show that notwithstanding the fact that even yet certain facts remain obscure, recent discoveries have permitted plausible explanations to be made of many formerly inexplicable occurrences. At first Wassermann<sup>30</sup> believed it most probable that the antigen was a soluble body standing in direct relation with the syphilitic agent (erreger). Weil and Braun<sup>32</sup> then denied the correctness of Wassermann's assertion that his experiments with paralytic sera had demonstrated the presence of specific anti-substances, antibodies related to the syphilitic antigen. By way of reply to this criticism Wassermann, in December, 1907, published an article<sup>29</sup> upon the development and present status of the serodiagnosis in syphilis. He first makes the point that the results obtained by the serodiagnostic method have been confirmed by clinical observations and autopsies, and that where the technic has been properly learned and carried out the results have been uniformly correct. He then goes on to say that disagreement as to the theory does not disprove the fact of the existence of the reaction. "Its nature is another matter. I merely say that it has to do with an antigen possessing some connection with a syphilitic process which is accompanied by the appearance in the syphilitic serum of a substance which we call an antibody or, speaking broadly, a reacting substance. Although I believe the spirocheta pallida to be the cause of syphilis, I will not go so far as to say that we have to do in this reaction with a direct reaction with the spirocheta pallida." <sup>29</sup> "The next step," he continues, "was the discovery, by Porges and Meier, first, that alcohol would give an extract of the syphilitic livers equal in results to the watery extract and, second, that the alcoholic extracts of normal livers would also give positive results." Starting from this point, Porges and Meier suspected that the soluble substance which was carried over into the extracts was a lipid body. They then demonstrated the fact by obtaining positive results with solutions of the lipid substance, lecithin. Therefore, Wassermann concludes, "further experiments are needed to show whether we are dealing with substances easily extracted by alcohol or with pure chemical substances like lecithin." This is the framework of the theory which has been strengthened here and there by the conclusions of others. It has already been mentioned that Bruck and Stern<sup>8</sup> were able to demonstrate that injections of syphilitic material (antigen) into apes was followed by an increase of antibodies in the serum. They concluded that while syphilitic antibodies were present in normal serum their increase was the indirect result of the stimulation of the syphilitic antigen. Hoffmann and Blumenthal,<sup>13</sup> and Landsteiner, Müller and Pötzl<sup>14</sup> express practically the same opinion although in slightly different terms. Citron<sup>9</sup> and Marie<sup>17</sup> are inclined to attribute the presence of antibodies in paralytic sera to changes in the

cells, thus agreeing in part with Weil and Braun.<sup>32</sup> Michaelis<sup>19</sup> seemed to anticipate events for, after agreeing with the view that it is doubtful if the reaction has anything to do with the syphilitic agent (erreger) or its toxin, he goes on to say that "it is not absolutely proved that there are not two reactions going on together, one with the syphilitic agent, the other with the albumens of the organs," a view in which he is supported by Seligmann.<sup>25</sup>

*Progress in theory.* — Beneke<sup>4</sup> presents histological evidence to support the opinion that possibly the reaction may be caused by a lipid substance. He states that he has noted for a long time that the livers of dead born syphilitic children are chiefly composed of large and small fat drops which Loeffler's methylene blue promptly stains deeply. The cause of this staining reaction, according to Beneke, is an otherwise invisible soap membrane which covers the drop. The fact, he says, can readily be confirmed by experiments with an artificial soap emulsion which will show the same reaction. On the other hand, the fat drops of a normal liver do not give this staining reaction to methylene blue but remain unstained. Beneke, therefore, looks upon these facts as evidence of maceration or autolysis, and states that the reaction is related to a similar staining of the fat drops produced by necrosis of the pancreas and which is occasionally encountered in single drops produced by inflammation of the fat tissue. This soap membrane belongs to the lipid group. "This histological fact shows, moreover, that the liver of the syphilitic new born is rich in soap, which, naturally, must go over into a watery as well as an alcoholic extract. It is very probable, therefore, that this body is the cause of the Wassermann reaction. This fact would not only support Michaelis' guess that there existed in syphilitic livers a substance which was either more abundant than in normal livers or else more easily extracted, but would also explain why an organ which has been kept for some time furnishes a more active extract than a fresh organ." This in turn would add weight to Wassermann's assertion that reliable results can be obtained only by the use of fresh extracts. Sachs and Altmann<sup>23</sup> tested the influence of alkalies and acids upon the behavior of the reaction in order to determine the possible rôle of the lipid substances. They found, on the one hand, that by adding an excess of alkali to the serum they could destroy the previous positive reaction and, on the other hand, that in several instances sera which previously gave a negative reaction became positive after the addition of hydrochloric acid. They concluded, therefore, that the chemical reaction of the sera was a factor in the presence or absence of the serum reaction. In addition to the theories already given, Bauer<sup>3</sup> advances the theory that the so-called antagonistic substances assist the lipoids to exercise the power of complement deviation.

*Conclusions.* — If we now sum up the foregoing reports it would seem that the theory which, in the light of our present knowledge, best explains

the serum reaction is that it is caused by a lipid substance; that this lipid substance is present in greater or smaller amounts in normal serum; that through the syphilitic infection the organism is stimulated to an increased production of antibodies; that the lipid substances are soluble in water and in alcohol. Finally, we may accept the fact of the reaction. We may conclude that while the Wassermann reaction is not specific, strictly speaking, it nevertheless appears to be clinically specific; that, therefore, in doubtful cases a positive reaction should be given weight in the diagnosis; that, on the other hand, a negative reaction tells us nothing. Much further investigation is needed, however, to tell us "as to the proportion of cases in which the reaction gives us accurate information."<sup>15</sup>

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## Reports of Societies.

## AMERICAN LARYNGOLOGICAL ASSOCIATION.

THIRTIETH ANNUAL CONGRESS, HELD AT MONTREAL,  
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(Continued from No. 15, p. 482.)

SECOND PAPER. THE ETIOLOGY OF PARALYSIS  
FROM PERIPHERAL CAUSES

was discussed by Dr. D. BRYSON DELAVAN, of New York. He made three general groups of cases: first, those due to trauma; second, those due to mechanical pressure on the nerve, and third, those due to some toxemia either from a poisonous substance taken into the body or from disease. The trauma would include gunshot and incised wounds of the neck, injuries arising from surgical operations and foreign bodies in the larynx or neighboring regions and unsuccessful attempts at removal. Mechanical pressure might be caused by disease of the glands or lymph nodes, tumors, aneurisms, diseases of the heart or pleura and scoliosis. Thyroid enlargement was a very common cause, but the size of this organ seemed to have little effect on or relation to the amount of danger inflicted on the recurrent nerves. Large ones might give no trouble; small ones might cause death. In the author's experience aortic aneurism has been the most frequent cause of left paralysis. From its position with regard to the apex of the right lung the right recurrent may be pressed on under certain pulmonary conditions. Some cases which have been ascribed to pressure in abnormal thoracic conditions may have been due to severe inflammatory states rather than to simple mechanical pressure. By far the most interesting group of cases is the third, viz., that due to toxemias. About these we know but comparatively little. Drugs and infectious diseases may both thus act. There may be a peculiar and distinct vulnerability of the recurrences to toxic effects. Of mineral and vegetable poisons mention was made of lead, arsenic, antimony, copper, iodide of potash, iodoform and perhaps cyanide of potash and phosphorus. Of vegetable poisons, mention was made of alcohol, opium, belladonna, cannabis indica and cocaine. The list of infectious diseases comprised typhoid fever, acute rheumatism, influenza, diphtheria, typhus, pneumonia, puerperal fever, erysipelas, measles, scarlet fever, gonorrhea and serum therapy. Our future knowledge along this line must come from a consideration of and a answer to the following propositions: (1) Is there any truth in the supposition that there is a selective affinity existing in these particular nerves (recurrences) in favor of certain particular drugs through the influence of which the one exercises an inhibitory effect upon the other? (2) Does the drug produce changes in the nerve tissue itself which result in the loss of its activity? (3) Is the lesion a neuritis, induced by pressure or congestion of neighboring parts or by other causes? and (4) Are the effects on the nerve due to central causes, the latter induced by the drug? The "affinity" doctrine seems to be contradicted by the fact that the cases are generally unilateral, not bilateral. The same objection applies to (4). In regard to pressure, it seems probable that this is the mode of action in many instances. The writer was not able to place absolute reliance on the recent statistics of Sendziak, as references were not given and his statements could not be verified nor could the articles from which he derived his material be studied.