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DIAGNOSIS AND TREATMENT OF SYPHILITIC AFFECTIONS OF THE ACOUSTIC NERVE, WITH SPECIAL REF- ERENCE TO THE USE OF SALVARSAN.*

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Within the last decade great advances have been made in elucidating the physiology and pathology of the eighth nerve and its end-organs. That Barany has been the master mind in this field is amply attested by the recent award to him of the Noble prize. Without question, contemporaneous progress has been made in other fields of medicine, particularly in sero-diagnosis, serotherapeutics and chemotherapeutics. Schaudinn, by isolating the spirochete pallida, Wassermann by perfecting his complement fixation reaction test, and Ehrlich by devising salvarsan probably have conferred the greatest boon of this generation on the profession and humanity in the scientific diagnosis and treatment of syphilis in its protean manifestations.

Diagnosis. With the recent renewal of interest, initiated by the investigations of Barany and other leading otologists, in the effort to solve various physiological problems of the acoustic mechanism and to facilitate accurate and scientific diagnosis and treatment of pathological conditions where disease has invaded the ear, particular attention has been directed to those cases associated with syphilis, especially those treated with salvarsan.

As you are well aware, since the advent of salvarsan as a panacea in lues, apparently there has been a marked increase in the fre-

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quency and severity of inflammatory reactions of the eighth and other cranial nerves. In the meantime there has been much discussion as to the nature and etiology of these reactions—whether due to the toxins of the spirochete pallida or to the toxic effect of the salvarsan. This disputed question we will refer to later. At present we wish to consider some early clinical diagnostic signs of syphilis as manifested in disturbances of the acoustic functions. Preliminary even to the period at which we may expect the positive Wassermann, that is, a month to six weeks following infection and previous to the appearance of any general symptoms, the otologist, by careful functional tests of the ear, is able in a majority of cases to arrive at an early diagnosis of syphilis.

Clinical signs—shortened bone conduction. A definite and often marked shortened bone conduction is almost always present in the initial primary stages of lues, notwithstanding that air conduction remains practically normal, particularly for the lower tones, provided there are no middle-ear complications from other causes. So constant, in fact, is this shortening, when tympanic conditions can be excluded, that it is regarded by some authorities as characteristic, if not pathognomonic, of lues, especially in the primary and secondary periods of the acquired type. It is also present not infrequently in hereditary syphilis.

Willcutt¹ cites Wanner and Oscar Beck as pioneers in the recognition of the great importance of this clinical sign, but credits Crockett with an earlier report of this condition though the latter failed to emphasize its clinical significance, contenting himself with calling attention to the relatively normal air conduction, notwithstanding the complete absence of bone conduction in the three cases reported. The amount of loss of bone conduction in these syphilitic cases varies greatly, ranging from a few seconds to almost total loss. For this reason the significance and reliability of the test has been questioned by some who claim that the age of the patient and the structure of the mastoid bone (whether pneumatic or sclerosed) may account for considerable variations in the bone conduction. Clinical experience, however, as evidenced by the reports of many investigators, has confirmed the earlier claims and demonstrated marked difference in the relative bone conduction in syphilitic and non-syphilitic cases. Willcutt¹ reports the findings of his examinations in about three hundred syphilitic cases in Urbantschitsch's Vienna clinic. In this series of cases there were fifty-eight cases of a month's duration or less. Fifty-two of these fifty-eight cases showed a definite shortening in the bone conduction though he was careful to exclude all

other conditions that might be responsible for the reduction. In six of these fifty-eight cases there was no diminution of the bone conduction. It is a fair deduction, judging from such reports, that in the primary stages of lues we may expect a definite reduction of the bone conduction in about 90 per cent of the cases. My experience certainly tends to corroborate the above high percentage.

Plus Rinne. With shortened bone conduction, the air conduction remaining nearly normal, we usually get a strong, positive Rinne in the early stages of syphilis. Should an acute middle-ear condition complicate, the previously lowered bone conduction may be elevated, but seldom to or beyond the "normal point." With the subsidence of the acute middle-ear trouble, the bone conduction returns to its original low level.

Theories of the causation of the lowered bone conduction. Two theories have been advanced to explain this condition. O. Beck² contends that it is due to an increased cerebrospinal pressure. Willcutt, Knick and Zaloziecki³ and others believe it is due to a toxic irritation or degeneration of the acoustic nerve. A combination of these causes, I believe, is a more plausible theory as to the etiology of this condition in a majority of the cases.

Beck bases his theory on his observation that following lumbar puncture in syphilitic cases the shortened bone conduction tends immediately, or soon, to resume the normal, but in a few days, with the return of the increased cerebrospinal pressure, it is gradually lowered again. That the increased cerebrospinal pressure may be a factor in the etiology of the lowered bone conduction in many cases, particularly in the secondary stages, hardly admits of doubt. The plausibility of this contention is augmented by the familiar and easily demonstrated effects of the reduction of the bone conduction in normal ears in performing the Gelle test. In the latter instance, of course, the counter pressure comes from without and is exerted indirectly through the drum. My experience in making functional tests in luetic cases confirms Beck's theory to the extent that the shortened bone conduction revealed by the Schwabach test is further reduced by the pressure occasioned by the Gelle test, provided there has been no fixation of the stapes, etc., by middle-ear complications.

Willcutt questions the plausibility of Beck's theory on the ground of the short duration of many of these cases of very early syphilis in which reduced bone conduction is present, the diagnosis of which has been authenticated by the demonstration of the spirochete pallida from smears of the primary lesion and a positive history of

infection. The argument is advanced that a syphilitic meningitis has not time to develop to a sufficient extent to produce a cerebro-spinal pressure adequate to materially lower the bone conduction. And when we consider that shortened bone conduction is an initial and almost constant symptom of lues, occurring as early as the eighth day, we are inclined to the opinion of Willcutt and others in the toxic theory. The basis of the latter theory in causing early shortening of bone conduction is that the toxins and endotoxins of the spirochete circulating in the blood affect primarily the most sensitive tissues—the brain, meninges, cranial nerves, etc.—which accounts for the early lesion of the acoustic, the meningeal headaches, and other “increased nerve reflexes” which frequently occur in the initial primary stages of syphilis. Therefore, given a shortened bone conduction, which is definite and marked in 90 to 95 per cent of syphilitic cases, even in the primary stages, with the air conduction remaining practically normal unless there has been or exists a middle-ear complication, a positive Rinne is a necessary corollary and a strong confirmatory test to the specificity of the auditory lesion. Kerrison,⁴ while conceding the diagnostic value of lowered bone conduction in these cases, differs from most authorities in his findings in the Rinne test, claiming it is negative, particularly in the latent stages. The following functional hearing tests may be regarded as strongly diagnostic of early syphilis:

1. Bone conduction definitely shortened.
2. Rinne positive.
3. Air conduction—low notes, relatively normal—high notes definitely lowered.
4. Bilateral affection.

However, in the advancing stages of syphilis the focal aural lesions may become suddenly augmented as evidenced by more or less intense and abrupt manifestations of an acute auditory neuritis. When the cochlear branch alone is involved, and it is usually the first to suffer, there is severe, constant tinnitus which is accompanied or soon followed by impairment of hearing varying in degree, from time to time, from slight to total deafness. If the invasion extends to the vestibular branch, which it usually does after a brief interval, the above acoustic disturbances are supplemented by even more distressing static disturbances, as vertigo, dizziness, nausea, vomiting, disturbed equilibrium, great prostration, etc.

To summarize, at this juncture, I would emphasize some important phenomena in the differential diagnosis of specific eighth nerve neuritis and inflammatory or suppurative labyrinthitis. The most

characteristic of these are the marked variations, often from day to day, both of the acoustic and the static manifestations in specific neuritis, together with the incidence that the severe attacks are frequently preceded by one or more milder attacks, whereas in inflammatory labyrinthitis the first attack is most severe and the acoustic and static symptoms are coincident, and remain permanent, or gradually ameliorate. Moreover, in specific neuritis not infrequently there is a short interval between the acoustic and static symptoms which is accounted for by reason of the greater vulnerability of the cochlear branch to the luetic toxin, therefore it is usually affected first. Wintermute⁵ explains the great variations of hearing in specific auditory neuritis as follows: "When the infiltration of the nerve is great, many of the fibres are incapacitated by pressure, and the patient hears badly; on other days the infiltration is absorbed, the pressure is reduced, and those fibres which are not degenerating recover their function, and the patient hears much better."

The vestibular branch reactions are of the labyrinthine type, and are equally or more vacillating than the acoustic, and their great variations probably may be explained by the same mechanism. The turning reaction is usually the first to go, the caloric following. However, one may be present and the other absent. Occasionally the labyrinth is so sensitive that it responds to the fistula test. Hill Hastings⁶ reports a case of hereditary syphilis of this type.

Treatment. The value of serum and vaccine diagnosis and therapy in many of the infectious diseases is now universally acknowledged, thanks to the distinguished services of Pasteur, Koch, Behring, Wright, Wassermann, Ehrlich, Flexner, Nogouchi, Dwyer and many other investigators working in bacteriological and immunological fields. The Wassermann reaction as applied to syphilis, is a brilliant example of the practical worth of serological *diagnosis*, but unfortunately, to date, we have no biological *therapeutic* product of equal value to heal this dreadful scourge. All hail, then, and all the more opportune Ehrlich's epoch-making discovery of a "therapia sterilizans magna," a *chemotherapeutic* product—salvarsan—which in the great majority of cases acts as a specific in the active immunization and cure of syphilis. But since the introduction of salvarsan in systemic specific therapy, unfortunately, perhaps unquestionably, there has been a relative increase in the frequency and severity of the focal reactions or so-called "neurorecidives" heretofore observed in the acoustic, facial and other cranial nerves, in syphilitic cases.

And this brings us to the consideration of the paramount question whether these focal reactions, or at least their greater fre-

quency and increased severity may be imputed directly to the toxic action of the salvarsan, or only indirectly to the provocative effect on the entrenched spirochetes in their respective foci, i. e., a provocative focal specific reaction similar to the provocative general specific reaction, indicated by the return of a positive Wassermann, sometimes observed in the administration of mercury, salvarsan or other antiluetic therapy.

A clear comprehension of this question can be obtained only by an analysis of the action of the *treponema pallidum* on the various tissues of the body in conjunction with the therapeutic mechanism of salvarsan in ridding the individual of this organism and its endotoxins. The literature abounds in citations of case reports relative to the frequency and severity of early syphilitic involvement of the acoustic nerve, both prior and subsequent to the use of salvarsan. The investigations of Benario, Habermann, Mayer, Frey, Riguad, Politzer and others show the not infrequent occurrence of syphilitic focal reactions or neurorecidives before the discovery of salvarsan. And, moreover, large clinical experience has shown that since the introduction of salvarsan it has been efficacious, if properly administered, in clearing up the focal lesions. Nevertheless, O. Beck, Finger, Alexander, Urbantschitsch, contend that the administration of salvarsan in luetic cases is not without danger, particularly if there is co-existent an inner-ear inflammation. Whether salvarsan therapy may be provocative rather than preventive and curative of this auditory lesion, occurring more or less frequently in the primary and secondary stages of syphilis, is still a mooted question which, finally, must be settled, I believe, by further studies and investigations along immunological lines, together, of course, with clinical experience. An elaborate discussion of immunology and therapy cannot be undertaken here, but a synopsis of salient features may not be out of order.

The mechanism of salvarsan therapy in syphilis is that of a vaccine. The mechanism of vaccine therapy in infectious diseases, as you well know, is based on nature's method of combatting pathogenic organisms invading the body. Wright has informed us that nature's way of resisting these organisms is through the opsonins normally present in the blood stimulating the phagocytes to the formation of antibodies which are antitoxic to that class of bacteria which secrete soluble toxins, and are bactericidal and bacteriolytic to that class of bacteria which elaborate within themselves endotoxins, the liberation of the latter in the circulation and the body tissues, however, being contingent on the destruction of the bacteria. The spirochete pal-

lida belong to the latter class. Dwyer⁸ emphasizes the point that these endotoxins are not necessarily and usually are not neutralized by the vaccines which liberate them. In view of the latter incidence, we would expect during the treatment of infectious diseases by vaccine therapy more or less decided and even violent reactions—general, focal and local, due directly to and dependent upon the character and amount of toxins introduced or freed. This is only too aptly illustrated in the tuberculin vaccine therapy of tuberculosis. The analogy may be applied to salvarsan therapy in syphilis. And since Ehrlich and Plaut have demonstrated that salvarsan has no tropic effect on the spirochete outside the body, we must conclude that when it is administered intravenously it forms with the blood plasma a biochemic product, or a biochemic vaccine if I may so designate it, which is bactericidal and bacteriolytic to all the spirochetæ in the circulation or in tissues or foci accessible to the circulating media. The immediate results following this wholesale destruction of the spirochetæ, with the liberation of their endotoxins are more or less decided general or systemic reactions and occasionally focal reactions. The former reactions are indicated by malaise, rise of temperature, chilliness or rigors, headache, nausea, vomiting, cramps, etc., while the latter reactions are evidenced by a disturbance or destruction of the functions of the organs or tissues in which the *treponema pallidum* may have a local habitation.

Etiologically, according to Thomas and Ivy,⁹ these clinical general reactionary effects of salvarsan therapy in syphilis “probably occur by virtue of two facts: Firstly, the endotoxins arising from the destruction of myriad numbers of spirochetæ, and, secondly, to the toxic effect of arsenic itself, based on personal idiosyncrasies.” The clinical focal reactions may be regarded as Herxheimer reactions which, according to the same authorities, are defined “as any inflammatory reaction in syphilitic tissue provoked by the administration of salvarsan, neosalvarsan or mercury.” Focal reactions probably occur by virtue of one factor—the direct action of the luetic endotoxins. These are freed either in the circulating media and conveyed by them to the seats of the focal reactions, else they are freed at the seats of the focal reactions. Therefore, salvarsan, or rather the non-toxic biochemical product it forms with the blood plasma to destroy the spirochaetæ and liberate their endotoxins, is only indirectly causative of the focal reactions. Moreover, Ehrlich’s laboratory experiments with injections of salvarsan in animals and examination of the nerves microscopically afterward, convinced him that salvarsan had no direct or selective toxic or neurotropic

action on the nerves. His theory as to the etiology of focal reactions or so-called "neurorecidives" following the injections of salvarsan in syphilitic cases is that while the spirochetæ in the general circulation are easily accessible to the tropic influence of the drug, those located in nerves may escape on account of the restricted vascularity—and the spirochetæ focussed in these points multiply rapidly, cause infiltration and swelling of the nerves which, if confined in narrow, bony canals as the eighth, seventh and some other cranial nerves, are subjected to the counter-pressure of these bony walls with the consequent disturbance or loss of nerve function. In case of a coaffection of several of the cranial nerves we get a syndrome designated as the Frankl-Hochwart's disease, or a polyneuritis cerebrealis.

The occurrence then, of focal reactions in the acoustic, facial or other cranial nerves during the course of salvarsan therapy, in syphilitic cases, is no incrimination of this remedy directly, but rather an indictment of the technique of administration. Either the dose has not been sufficiently large, else not repeated sufficiently often and continued sufficiently long to completely destroy all the spirochetæ pallida, particularly those in avascular foci—as nerve tissue, or in other foci or recesses difficult of access—as the cerebrospinal fluid. When properly given we may safely acquit salvarsan of producing neurotropic lesions, as "neurorecidives," but we cannot emphasize too strongly that its safety and efficiency in preventing and curing such syphilitic lesions depend upon its timely and intelligent administration; controlled by repeated examinations not only of the blood but of the cerebrospinal fluid.

Report of cases. The appended case reports are fairly typical of the acoustic clinical manifestations and focal reactions occurring in syphilitic cases, particularly those that have been neglected or inefficiently treated.

Case 1. Mr. T. E. B., age 31, was referred November 10, 1915, on account of almost total deafness. The following history was elicited. He noticed chancre July 1, 1914. His local doctor gave him pills, perhaps protiodide mercury, for about one month. Following this he had mercury injections twice a week until May 1, 1915. In the meantime he had two injections of salvarsan, the first late in November, 1914, and the second late in January, 1915. First Wassermann was made in February, 1915, during treatment which, of course, proved negative. All treatment was suspended May 15, 1915. June 30, 1915, he suffered a left facial paralysis and total deafness on that side. At the time he was very dizzy, had difficulty

in walking and was compelled to keep his head straight forward to avoid falling. In two or three weeks the facial paralysis had about cleared up, the dizziness disappeared and the disturbed equilibrium readjusted itself. July 15 he suffered total loss of hearing in the right ear. From this date he resumed treatment with mercury bichloride grs. 1/10 t. i. d. in combination with kali iodid, beginning with grs. V. and increasing doses up to grs. XL. t. i. d. This was continued till I saw him November 10, 1915.

Functional ear tests at that date revealed the following acoustic and static conditions. With noise apparatus in right ear—total deafness in left ear. The low note for fork in right ear was small E (2) and the high note was 5.9 Galton. There was no spontaneous nystagmus. Turning ten times to left, with head inclined forward 60°, produced rotatory nystagmus to the right for 12 seconds. Turning ten times to right, with head inclined forward 60°, produced rotatory nystagmus to left for 15 seconds. The caloric tests proved negative to heat of 118° F. Cold in the right ear produced violent nystagmus to the left of 1 m. and 50 seconds' duration; and cold in the left ear produced nystagmus to right for 1 m. and 3 seconds.

Further treatment of this case by a competent syphilographer, though strenuous, was unsuccessful, only a slight improvement in the hearing was effected and this but temporary.

This case clearly illustrates the ill effects of delayed and inefficient treatment and the nonresponsibility of salvarsan in causing the neurorecidives. It was five months after the initial lesion before the first salvarsan injection and seven months before the second. It was five months after the second salvarsan before the occurrence of focal lesions in the seventh and eighth nerves on the left. The local lesions in the right ear followed two weeks later. In fact, all treatment had been suspended six weeks prior to the focal ear lesions. As salvarsan is rapidly eliminated from the system it could in no wise be responsible, directly or indirectly, for the focal ear lesions in this case. In fact, had salvarsan been given promptly in adequate dosage I am satisfied his ear lesions would never have occurred.

Case 2. This case is cited to illustrate the significance of shortened bone conduction as a reliable diagnostic sign of lues. Miss M. B., age 23, a stenographer, was referred December 22, 1915, on account of an anterior subluxation of the septal cartilage obstructing nasal breathing on the left. She said she had been troubled with catarrh as long as she could remember and for some time had noticed some stuffiness in her ears. It occurred to me that the latter symptoms were due indirectly to the nasal obstruction and that the

correction of this would relieve the middle-ear complication. However, this hoped-for result did not occur. A careful functional test revealed, to my surprise, a marked reduction in the bone conduction—18 sec. in the right and 14 sec. in the left, notwithstanding the mild middle-ear catarrh. This aroused my suspicion of lues and I went into her family history. Father died at the age of 68 from apoplexy; mother died at the age of 52 from cancer, but had suffered a right facial paralysis three years before her death. She has two brothers, both healthy; one younger sister, 19 years old, has a goitre. Her personal history, as regards lues, according to patient's statement, is negative. She had a left facial paralysis two and a half years ago and for three days preceding the facial paralysis she had twitching of the facial muscles on the left, was dizzy and had difficulty in walking. Following the facial paralysis she had about a week's treatment with a "salty solution" and this with massage cleared up the paralysis in about six weeks. She complains of extreme fatigue and for the past six or seven years has been troubled with somnolence—nodding, sometimes she says, while taking dictation. Her general appearance is good. However, the shortened bone conduction, in spite of the middle-ear catarrh, taken in connection with the history of the left facial paralysis and her somnolence, induced me to refer her for a Wassermann which, not to my surprise, proved three plus. The diagnosis of lues was returned.

Other reports could be cited from my case books but these are sufficient to illustrate the claims of the text.

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