

## METHODS FOR THE REACTIVATION OF NEGATIVE FLUIDS IN NEUROSYPHILIS

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One may observe cases, although they are extremely rare, of paresis in which the Wassermann reaction is negative in the cerebrospinal fluid, or only faintly positive, even with large amounts of fluid. This finding is much more frequent, of course, in cases already treated and in cases of tabes in which the cerebrospinal fluid shows hardly any alteration. At times these patients prove to be difficult diagnostic problems, especially when the clinical picture is not unequivocal.

Dattner says that, with large amounts of fluid, a positive Wassermann is present in tabes in 95 per cent of cases; but Bodechtel points out that, on the basis of his experience in the Neurological Policlinic in Hamburg, in only 60 per cent of cases at the most could a positive reaction be obtained. (See the detailed bibliographic reference of Georgi on cases of tabes with negative fluids.)

Further, these cases invalidate the rule on which Dattner insisted so strongly, that a negative fluid five years after infection, appears to remain negative. In tabes, the fluid remains negative for many years; one does not know whether it has been positive at some time, although probably this occurred in the period comprehended between the second and fifth year of infection. In these cases the diagnosis may be made only clinically. One usually deals with cases of tabes of a slow, stationary course; Wagner V. Jauregg used to call them "tabes peracta," meaning by this that the active period of the tabes had already elapsed. The French refer to these cases as "tabes fixé, non évolutive." However, even this criterion cannot be upheld in the category of an absolute rule. In one of our cases, tabes began in a more or less acute way, with intense lancinating pains, but the spinal fluid was negative, notwithstanding the opinions of Alajouanine and Marquezy, who consider that the most valuable symptoms for diagnosis of the activity of tabes are lancinating pains.

In the course of already wide experience in the treatment of paresis and other forms of neurosyphilis with penicillin, we had repeatedly observed that the injection of this antibiotic in the subarachnoid space

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was capable of intensifying, in a transitory way, the pathologic reactions in the cerebrospinal fluid of ill people in whom penicillin treatment had produced first of all an improvement or even a complete negativity of the humoral syndrome in the fluid. This intensification of the reactions extends to all of them, but particularly affects the number of cells, the quantity of proteins and the Wassermann reaction.

It is known that the intrathecal administration of penicillin produces a meningeal irritation, with an increase in the number of cells and the quantity of proteins. What we have not seen described in the literature is the fact that, because of the intraspinal injection of penicillin, the Wassermann reaction, which formerly was negative, should become positive. This observation aroused our interest and made us consider the possibility of using the intraspinal injection of penicillin for clarifying the diagnosis in doubtful cases in which the examination of the cerebrospinal fluid does not allow of definite conclusions respecting the etiology of the pathologic process. Up to this date we have successfully used this method in a case of paresis and in 2 cases of tabes.

#### CASE REPORTS

*Case 1.*—A 72 year old man, in August 1947, began to show psychic disorders in the form of delusions of autoreference. After attempted suicide by drowning, he manifested a delirious picture, which ceased on his entry to our Clinic. Here he showed a deficit in memory and intellectual faculties, and no pupillar reaction to light, without other neurologic alterations. The reactions of Wassermann, Kahn, and Meinicke on the blood, done on the 21st and repeated on Oct. 31st, gave a completely negative result. Examination of the cerebrospinal fluid on the 22nd of the same month gave the following result: White cells per cubic mm.: 5. Red cells per cubic mm.: 5. Total proteins: 22 mg. per cent. Pandy: +---. Nonne-Apelt: negative. Weichbrodt: negative. Colloidal gold test: 1121000000. Wassermann reaction (Kapsenberg): doses of 1 cc.: ++---; doses of 0.5 cc.: negative; doses of 0.3 and 0.1 cc.: negative. After three days' consecutive administration of penicillin intraspinally, in doses of 15,000, 20,000, and 25,000 units, the examination of the cerebrospinal fluid was repeated with the following result: White cells per cubic mm.: 45; red cells per cubic mm.: 190. Total proteins: 44 mg. per cent. Pandy: +---. Nonne-Apelt: +---. Weichbrodt: +---. Colloidal gold test: 1121100000. Wassermann reaction (Kapsenberg): doses of 1 cc.: ++++; doses of 0.5 cc.: ++++; doses of 0.3 cc.: +++-; doses of 0.1 cc.: +---.

*Case 2.*—A 59 year old man, presenting a fairly clear clinical picture of dorsal tabes; owing to the complete negativity of the cerebrospinal fluid, repeatedly examined, and the strange disorders of the sensibility that were apparent, other clinicians began to think there might be a possibility of syringomyelia. After intraspinal penicillin injection during six consecutive

days in doses of 15,000, 20,000, 25,000, 30,000, 30,000 and 30,000 units, examination was repeated of the cerebrospinal fluid, with the following result: Liquid slightly xanthochromic, somewhat opaline. White cells per cubic mm.: 165. Red cells per cubic mm.: 5. Cytologic formula: Polynuclears: 88 per 100. Transitionals: 1 per 100. Eosinophils: 3 per 100. Lymphocytes: 8 per 100. Total proteins: 44 mg. per 100. Globulins: 22 mg. per 100. Albumin: 22 mg. per 100. Pandy: +---. Nonne-Apelt: +---. Weichbrodt: +---. Colloidal gold test: 2234544320. Wassermann reaction (Kapsenberg): doses of 1 cc.: +++++; doses of 0.5 cc.: +++++; doses of 0.3 cc.: +---; doses of 0.1 cc.: negative.

*Case 3.*—A man, 56 years of age, in whose case the onset was characterized by pains in the legs in 1937, disappearing on treatment with novalgin. Months afterward the pains returned, and were treated anew with symptomatic medication. In 1941, a new painful phase with hiccough. During this year, apparition of the pains from the lancinating type all through his legs. Round pupil, small. Robertson, knee, and Achilles reflexes almost absent. Hypotonia. No Romberg. Sensibility for numbers maintained as well as sensibility to vibrations and position. Perpetual arrhythmia. Wassermann, Meinicke, and Kahn in blood, positive. Fluid analyzed on Nov. 24th, 1947:—Transparent liquid, colorless, like water. Red cells per cubic mm.: 11. White cells per cubic mm.: 2. Total proteins: 29 mg. per 100. Nonne's reaction: +---; Pandy's reaction: +---; Weichbrodt's reaction: negative. Colloidal gold test: 1112321000. Wassermann reaction: doses of 1 cc.: negative; doses of 0.5 cc.: negative; doses of 0.3 cc.: negative; doses of 0.1 cc.: negative. Intraspinal penicillin injections beginning with 5,000 and continuing with 10,000, 15,000, 20,000, and 30,000 units. No meningeal reaction visible clinically. During the penicillin treatment the violence of the pains increased extraordinarily. Second analysis of fluid, on Dec. 1, 1947: colorless and transparent fluid. Red cells per cubic mm.: 5. White cells per cubic mm.: 16. Total proteins: 44 mg. per 100. Albumin: 37 mg. per 100. Globulins: 7 mgr. per 100. Pandy's reaction: +---. Nonne-Apelt's reaction: +---. Weichbrodt's reaction: ---. Curve of colloidal gold: 1-1-2-3-1-0-0-0-0-0. Wassermann's reaction (Kapsenberg): doses of 1 cc.: +---. Doses of 0.1 cc.: +---.

A possible interpretation of these facts might be that the meningeal irritation produced by the penicillin increases the permeability of the blood-liquid barrier, and thus permits the passage of syphilitic reagins to the cerebrospinal fluid. But this possibility is discarded if we consider that in some of our patients the Wassermann reaction on the blood was constantly negative.

On the other hand, not always in a meningeal reaction in an ill person with a positive Wassermann reaction, does one obtain a positive Wassermann reaction on the fluid, as the following clinical history shows:—

*Case 4.*—A patient, 59 years old, with luetic antecedents and a demential psychiatric picture, suspected of paresis, but with no neurologic disorder apart from a lazy reaction of the pupils to light. The serologic findings in the blood, carried out on Oct. 29, 1947 gave the following result. Wassermann (heated serum): +++++; Kahn: +++—; Meinicke (M.K. R.II.): +++—; Meinicke (M.T.R.): +++—. Examination of the cerebrospinal fluid made on Nov. 4th gave the following results: Red cells per cubic mm.: 5. Total proteins: 22 mg. per 100. Pandy: +——-. Nonne-Apelt: negative. Weichbrodt: negative. Curve of colloidal gold: was not tried. Wassermann reaction (Kapsenberg), doses of 1 cc.: negative; doses of 0.5, 0.3 and 0.1 cc.: negative. During six days of the week, up to a total of 12 days, penicillin was injected intraspinally in doses not exceeding 30,000 units. At the end of this period, an intense meningeal reaction was revealed, and the examination of the cerebrospinal fluid, extract of 4-12-1947, obtained the following result: Total cells per cubic mm.: 7,200. White cells per cubic mm.: 6,400. Total proteins: 88 mm. per 100. Albumin: 33 mg. per 100. Globulins: 55 mg. per 100. Pandy: +++—. Nonne-Apelt: +——-. Weichbrodt: +++—. Colloidal gold test: 1111222110. Wassermann reaction: negative, with doses of 1, 0.5, 0.3, and 0.1 cc. An examination of the cerebrospinal fluid was repeated 15 days afterward, without administering penicillin during this interval, and the clinical meningeal reaction had already disappeared, with the following result: White cells per cubic mm.: 40. Total proteins: 33 mg. per 100. Albumin: 26 mg. per 100. Globulins: 7 mg. per 100. Pandy: +——-. Nonne-Apelt: +——-. Weichbrodt: +——-. Colloidal gold test: 1124432110. Wassermann reaction (Kapsenberg): negative, with doses of 1, 0.5, 0.3, and 0.1 cc.

These facts give rise to the question as to the origin of the Wassermann reaction on the cerebrospinal fluid. On the one hand, observations speak in favor of a positive Wassermann in the fluid not coming from the Wassermann in the blood, owing to an alteration in the permeability of the blood-fluid barrier; on the other hand, many other facts, for example the above mentioned ones, speak in favor of the autochthonous origin of Wasserman on the fluid. This intramural origin is especially shown in the cases of Riebelin, Nonne, and Demme. In Demme's case, a cancerous metastasis revealed in a case of tabes with a negative Wasserman reaction on the blood and fluid, provoked a spinal block. The cisternal liquid continued to show negative reactions; meanwhile the lumbar under the block gave a positive reaction.

It is not well known what conditions create a favorable atmosphere for this positivity. One cannot assume, even in the cases treated with penicillin, that it is the simple increase of albumin and globulins, because the blood serum, in higher quantities, continues to be Wasserman-negative.

These penicillin reactivations create an interesting problem, that is, the necessity of continuing with the treatment, or starting with a new one, even though activity symptoms are absent, if the reactions on the activated fluid show some alteration. Our experience is yet too small on this point for us to make any statement one way or the other; but our impression is that in cases of paresis, one must watch and even insist on treatment while the reactivation occurs. In cases sufficiently treated, as for example, the following one, intraspinal penicillin does not produce reactivation.

*Case 5.*—A 40 year old patient, with a clinical picture of general paralysis of more than three years' duration. Intensively treated with malaria and Neo. Examination of the fluid made on Dec. 2, 1947 gave the following result: White cells per cubic mm.: 4. Total proteins: 44 mg. per 100. Pandy: +---. Nonne-Apelt: +---. Weichbrodt: +---. Colloidal gold test: 111233320. Wasserman reaction: negative in all doses. After intraspinal penicillin injections for six days in doses not exceeding 30,000 units, the analysis of the fluid was repeated with the following result: White cells per cubic mm.: 470. Total proteins: 66 mg. per 100. Albumins: 22 mg. per 100. Globulins: 44 mg. per 100. Pandy: ++---. Nonne-Apelt: +---. Weichbrodt: +---. Colloidal gold test: 111234420. Wassermann reaction (Kapsenberg): negative in all doses.

On the other hand, the same criterion cannot be maintained in tabes because of the special characteristics of its course. In the second case, it stayed stationary, in spite of new treatments not being carried out, and in spite of the fact that penicillin had obtained the appearance of Wassermann in the fluid, which never had been positive.

#### CONCLUSION

Penicillin administered intraspinally causes a positive Wassermann reaction, when previously it had been shown as negative, thus confirming the clinical diagnosis of neurosyphilis. This reactivation has a special interest because we may suspect the persistent activity of the process, yet not revealed.

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