Provocative Reactions in the Cerebrospinal Fluid in Neurosyphilis

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The provocative arsphenamin reaction in the blood is a familiar phenomenon. In many clinics, when a patient suspected of having syphilis gives a negative Wassermann reaction, an injection of arsphenamin is given; then the blood is tested at daily intervals thereafter, because it apparently has been shown that after the injection of arsphenamin the Wassermann reaction will be positive in some cases.

It is our purpose to call attention to a similar reaction taking place in the spinal fluid. We report several cases in which, after either intravenous or intraspinal injections, a negative spinal fluid became positive, or the positive pathologic findings were intensified. From the clinical standpoint, the phenomenon of intensification of symptoms relating to the central nervous system has frequently been described as occurring after treatment. To this phenomenon the term neuroreoccurrence has been applied. One is not sure in these cases whether the resulting intensification of symptoms is due to the introduction of the drug or whether it is a mere coincidence that an increase of symptoms appears following the injection. However, in relation to secondary syphilis, the intensification of symptoms following arsphenamin injection has occurred so frequently that it has been considered as due to liberation of toxins resulting from the lytic action of arsphenamin on the spirochetes. This is the so-called Herxheimer reaction. If this can occur in skin lesions, there is every
reason to suppose, a priori, that the same thing may occur in neuro-
syphilis. However this may be, the following cases would appear to
show that following intravenous and intraspinal injections of arsphen-
amin or arsphenamized serum, the spinal fluid findings may become
more strongly positive.

REPORT OF CASES

CASE 1.—History.—F. H., aged 36, according to the history obtained from
the patient, had experienced a sudden paralysis of the right leg and arm about
eighteen months previous to his admittance to the clinic. He recovered from
this in about two days. At the time his physician gave him a liquid medicine
(potassium iodid?). During the three months preceding his admittance to the
clinic he had been receiving intramuscular injections of mercury. He denied
syphilitic infection, but admitted exposure. He also admitted excessive use
of alcohol. He had been married five years. His wife was living and well,
but had never been pregnant. At the time of admittance he complained of
headaches, some loss of memory and a mild speech defect at times. The vis-
ceral examination revealed nothing abnormal.

Examination.—Neurologic: The pupils were equal and reacted to light. The
left patella and biceps reflexes were more active than the right. Abdominal
and cremasteric reflexes were normal. There were no abnormal reflexes.
Muscle strength in the legs and arms was good. Station and gait were nor-
mal. Ophthalmoscopic examination showed a few vitreous opacities, but the
disk and choroid were normal.

Mentally he seemed somewhat euphoric, boasting with great confidence of
his abilities. No definite memory disorder or speech defect was noted.

The Wassermann reaction was negative on the blood and spinal fluid; the
other spinal fluid tests, including cell count, globulin, albumin, and colloidal
gold reaction, were negative.

There was a difference of opinion as to the diagnosis, some members of
the staff diagnosing the case as neurosyphilis despite the negative laboratory
findings. Because of this difference of opinion, the patient was given a
provocative injection of arsphenamin. The blood was drawn at intervals of
twenty-four, forty-eight and seventy-two hours after the injection; all tests
were reported as negative. The spinal fluid was drawn some time later and
gave the following reactions: Wassermann reaction positive with 1 c.c. and
0.8 c.c.; negative with 0.6 c.c. and with the higher dilutions. There were 53
cells per cubic millimeter; globulin was present; and albumin was present in
excess. The colloidal gold reading was 244333000.

We may assume then, that a provocative reaction in the spinal fluid occurred
as a result of the intravenous injection of arsphenamin, the reactions which
had previously been negative becoming positive. This provocative reaction
did not appear in the blood.

Blood and Spinal Fluid Reactions.—The following reactions were obtained
before treatment: Wassermann reaction of the blood, negative; Wassermann
reaction of the spinal fluid, negative; globulin, 0; albumin, normal; cells,
0 per cubic millimeter; colloidal gold test, negative. After one intravenous
injection of arsphenamin was given the reactions obtained were: Wasser-
mann reaction of the blood, negative; Wassermann reaction of the spinal fluid, 55— — — — (positive); globulin, 2; albumin, 2; cells, 53 per cubic millimeter; colloidal gold curve, 244330000.

Case 2.—History.—This patient came under observation in the routine follow-up of the families of our known syphilitic patients. His wife was suffering from general paresis. Both denied any history of infection, although some years before a stillbirth had led to a diagnosis of syphilis, and a small amount of treatment had been given to both husband and wife.

Examination.—When examined the patient was in good health, and the only significant symptom was an inequality of the pupils. The Wassermann reaction of the blood was negative, but in view of the inequality of the pupils, a lumbar puncture was performed. This showed a Wassermann reaction positive with 1 c.c. of fluid, but negative with the higher dilutions. Globulin was absent; albumin was present in normal amounts; there were 9 cells per cubic millimeter and the colloidal gold reaction was negative. This test was repeated with similar results. Six injections of arsphenamin were then given over a period of some months. Five months later another spinal fluid examination was made. This again gave a positive Wassermann reaction with 1 c.c., 0.7 c.c., and 0.5 c.c. of spinal fluid. No cells were found in the specimen examined. Globulin was not obtained, and the albumin was present in normal amounts. The colloidal gold reaction was again negative. Thirteen injections of arsphenamin were given in the next ten months, and a spinal fluid examination at this time showed a positive Wassermann reaction with 1 c.c., 0.7 c.c., and 0.5 c.c. of spinal fluid. Globulin was present; there was an increase of albumin; and a pleocytosis of 25 cells per cubic millimeter was found. The colloidal gold reaction gave a strong parctic curve, reading 555443211.

Treatment and Course.—In the following eleven months, twenty-four injections of arsphenamin were given. At this time, the spinal fluid gave a doubtful Wassermann reaction, that is, there was a partial inhibition of hemolysis with 1 c.c. of spinal fluid, 0.8 of a c.c. giving a negative reaction. There were 4 cells per cubic millimeter; globulin was present in small amounts, and albumin was slightly increased. The colloidal gold reading was 1143210000, a reaction typical for cerebrospinal syphilis. The patient was given an injection of arsphenamin, and an intraspinal injection of Swift-Ellis serum, fortified by $\frac{1}{5}$ mg. of arsphenamin. Two weeks later, another specimen of spinal fluid was examined. The Wassermann test was not made. The cell count was normal. There was a slight amount of globulin, and a small increase in the albumin. The colloidal gold reaction was 1112100000, an almost negative reaction. This examination was followed by two injections of arsphenamin and one intraspinal injection similar to the previous one.

Blood and Spinal Fluid Reactions.—The reactions obtained Aug. 17, 1917, before treatment were: Wassermann reaction of the blood, negative; Wassermann reaction of the spinal fluid, 5 — — — — (positive); globulin, 0; albumin, normal; cells, 9 per cubic millimeter; colloidal gold test, negative. After six intra-

1. The Wassermann reaction on the spinal fluid is performed on titrated quantities varying from 1 c.c. to 0.05 c.c. The figure 5 represents strongly positive and a dash (—) a negative reaction. Each figure or dash represents the reaction for a certain dilution, the figure at the left representing the reaction with 1 c.c. of fluid, the second figure in 0.8 c.c., the third in 0.6 c.c. and so on in diminishing amounts. When a zero occurs it means that the test was not made in the dilution represented by its position.
venous injections of arsphenamin the reactions obtained Jan. 18, 1918, were: Wassermann reaction of the blood, negative; Wassermann reaction of the spinal fluid, 5541 — (positive); globulin, 0; albumin, normal; cells, 0 per cubic millimeter; colloidal gold test, negative. After fourteen intravenous injections of arsphenamin the reactions obtained Nov. 9, 1918, were: Wassermann reaction of the blood, negative; Wassermann reaction of the spinal fluid, 555000 (positive); globulin, +; albumin, ++; cells, 25 per cubic millimeter; colloidal gold test, 555443211. After twenty-six intravenous injections of arsphenamin the reactions obtained Oct. 21, 1919, were: Wassermann reaction of the blood, negative; Wassermann reaction of the spinal fluid, 3—0000 (doubtful); globulin, +; albumin, +++; cells, 4 per cubic millimeter; colloidal gold test, 1143210000. After two intravenous injections of arsphenamin and one intraspinal injection of arsphenamized serum the reactions obtained Nov. 8, 1919, were: Wassermann reaction of the blood, negative; Wassermann reaction of the spinal fluid, unsatisfactory; globulin, +; albumin, +; cells, 2 per cubic millimeter; colloidal gold test, 1112100000. After three intravenous injections of arsphenamin and one intraspinal injection of arsphenamized serum the reactions obtained Dec. 16, 1919, were: Wassermann reaction of the blood, negative; Wassermann reaction of the spinal fluid, negative; globulin, 1; albumin, 1; cells, 28 per cubic millimeter; colloidal gold test, 5445410000. After six intravenous injections of arsphenamin the reactions obtained April 17, 1920, were: Wassermann reaction of the blood, negative; Wassermann reaction of the spinal fluid, negative; globulin, 1; albumin, 1; cells, 5 per cubic millimeter; colloidal gold test, 3333320000. After two intravenous injections of arsphenamin and one intraspinal injection of arsphenamized serum the reactions obtained May 4, 1920, were: Wassermann reaction of the blood, negative; Wassermann reaction of the spinal fluid, negative; globulin, 2; albumin, 1; cells, 4 per cubic millimeter; colloidal gold test, 5555310000.

Case 3.—History.—This patient was seen first in the ataxic state of tabes dorsalis. He gave no history of syphilitic infection, but had been complaining of weakness in the legs and general malaise for about two years. He had been given twelve intravenous injections of arsphenamin at a local dispensary.

Examination.—This showed a classic picture of advanced tabes dorsalis. The pupils were unequal and gave the Argyll Robertson reaction. There was a paresis of the left external rectus muscle. Knee jerks and ankle jerks were absent. The patient was practically bedridden. The Wassermann reaction was negative for the blood and spinal fluid. There were 5 cells per cubic millimeter in the spinal fluid, a slight amount of globulin, and a slight increase of albumin. The colloidal gold reaction was essentially negative, 0000110000.

Treatment and Course.—He was given an intraspinal injection of Swift-Ellis serum, reinforced by 0.0002 gm. of arsphenamin, and one intravenous injection of arsphenamin. The spinal fluid examination two weeks later gave a positive Wassermann reaction down to 0.3 of a c.c. Globulin was absent; albumin was present in normal amounts; there were 3 cells per cubic millimeter, and the colloidal gold reaction was again essentially negative, 0001200000.

Another intraspinal injection of the same type as the previous one and four intravenous injections of arsphenamin were given, and in six weeks the spinal fluid was again examined. The Wassermann reaction was doubtful; a slight amount of globulin was present; albumin was increased; there were 3 cells per cubic millimeter, and a fairly strong colloidal gold reaction, 4432210000. Another intraspinal injection of Swift-Ellis serum, reinforced by 0.0001 gm. of arsphenamin and five intravenous injections of arsphenamin
were given, and five weeks later the spinal fluid showed a positive Wassermann reaction with 0.5 of a c.c.; one cell per cubic millimeter; globulin was present; albumin was increased; and a colloidal gold reaction of 433210000 was obtained. The intraspinal treatment was repeated, reinforcement of arsphenamin being by 0.0003 gm., and another fluid examination was made three weeks later. The Wassermann test was positive with 1 c.c. and moderately positive with 0.7 c.c. and 0.5 c.c. There were 9 cells per cubic millimeter; globulin was present; albumin was increased; the colloidal gold reaction was 433210000. In the following two months, two further intraspinal treatments were given of the same type as the last, and the spinal fluid again showed a positive Wassermann reaction with 1 c.c. and 0.7 c.c., and doubtful reactions with 0.5 c.c. and 0.3 c.c. There were 6 cells per cubic millimeter; globulin was present; albumin was increased; and the colloidal gold reaction was 112310000.

Blood and Spinal Fluid Reactions.—The reactions obtained before treatment, June 7, 1919, were: Wassermann reaction of the blood, negative; Wassermann reaction of the spinal fluid, negative; globulin, +; albumin, +; cells, 5 per cubic millimeter; colloidal gold test, 0000111000. After one intraspinal injection of arsphenamized serum and one intravenous injection of arsphenamin the reactions obtained, June 21, 1919, were: Wassermann reaction of the spinal fluid, 5555 — (positive); globulin, 0; albumin, normal; cells, 3 per cubic millimeter; colloidal gold test, 0001200000. After one intraspinal injection of arsphenamized serum and four intravenous injections of arsphenamin the reactions obtained, Aug. 2, 1919, were: Wassermann reaction of the spinal fluid, 5555 — (positive); globulin, +; albumin, +; cells, 3 per cubic millimeter; colloidal gold test, 4332210000. After one intraspinal injection of arsphenamized serum and five intravenous injections of arsphenamin the reactions obtained, Sept. 9, 1919, were: Wassermann reaction of the spinal fluid, 5551 — (positive); globulin, +; albumin, +; cells, 1 per cubic millimeter; colloidal gold test, 4333210000. After one intraspinal injection of arsphenamized serum and one intravenous injection of arsphenamin the reactions obtained, Sept. 27, 1919, were: Wassermann reaction of the spinal fluid, 543 — — (positive); globulin, +; albumin, +; cells, 9 per cubic millimeter; colloidal gold test, 4432210000. After three intraspinal injections of arsphenamized serum the reactions obtained, Nov. 21, 1919, were: Wassermann reaction of the blood, negative; Wassermann reaction of the spinal fluid, 5532 — — (doubtful); globulin, 0; albumin, 1; cells, 4 per cubic millimeter; colloidal gold test, 112210000. After one intravenous injection of arsphenamin and one intraspinal injection of arsphenamin and one intravenous injection of arsphenamin the reactions obtained, Jan. 11, 1920, were: Wassermann reaction of the blood, negative; Wassermann reaction of the spinal fluid, 4 — — — (doubtful); globulin, 0; albumin, 0; cells, 4 per cubic millimeter; colloidal gold test, 1111100000. After one intravenous injection of arsphenamin and one intraspinal injection of arsphenamized serum the reactions obtained, Feb. 21, 1920, were: Wassermann reaction of the blood, negative; Wassermann reaction of the spinal fluid, negative; globulin, 0; albumin, 1; cells, 5 per cubic millimeter; colloidal gold test, 1122100000. After one intravenous injection of arsphenamin and one intraspinal injection of arsphenamized serum the reactions, March 20, 1920, were: Wassermann reaction of the blood, negative; Wassermann reaction of the spinal fluid, negative; globulin, 1; albumin, 1; cells, 4 per cubic millimeter; colloidal gold test, 1123210000. After one intra-
Case 4.—History.—This patient gave a history of a chancre twenty years ago, which was burned with caustic. No secondary symptoms appeared, and he had no further treatment. Nothing of importance occurred until six months ago, when he began to feel dizzy, complained of sharp, shooting pains in the right arm and leg and severe frontal headache, which kept him awake at night. He was also quite dizzy. A short time later he had an attack, which left him weak on the right side, and about a month later his speech became thick. Impotence came on about this time. He went to a local dispensary where he was given fourteen injections of arsphenamin at weekly intervals. When seen by us, he was complaining of about the same symptoms, except that his dizziness was less marked and his headache had disappeared. In addition, he had difficulty in swallowing, “things going down the wrong way,” and he was short of breath.

Examination.—The pupils were small, about equal in size and reacted sluggishly to light. There was no nystagmus or strabismus and no diplopia. The right side of the face was drawn up slightly. The tongue protruded in the midline. The right half of the palate was not raised as well as the left. There was a dysarthria; test phrases were pronounced a little heavily and with slurring. The arm reflexes were sluggish, but the right reflex was more pronounced than the left. The knee jerks and ankle jerks were absent. The patient walked with a slight ataxia, and there was marked swaying in the Romberg position. There was subjective numbness of the right hand but no objective sensory disorder. The Wassermann reaction was negative for the blood and spinal fluid. There were no cells in the cubic millimeter of fluid examined; globulin was not present; albumin was present in normal amounts; the colloidal gold reaction was essentially negative, 0009001110.

Course and Treatment.—He was given an intraspinal injection of Swift-Ellis serum, reinforced by 0.0002 gm. of arsphenamin, and five intravenous injections of arsphenamin. The spinal fluid examination, six weeks after the intraspinal injection, showed 13 cells per cubic millimeter. Globulin was present; albumin somewhat increased, and there was a paretic colloidal gold reaction, 5555431006. The Wassermann reaction on the spinal fluid was not done. He was given another intraspinal injection and four intravenous injections. The Wassermann reaction was negative; globulin was present in small amounts; albumin was increased; and the colloidal gold reaction was 5444321000. Another intraspinal injection of Swift-Ellis serum, reinforced by 0.0005 gm. of arsphenamin, was given, and five weeks later the spinal fluid was again examined, showing a negative Wassermann reaction; 1 cell per cubic millimeter; globulin was present; albumin was increased, and the colloidal gold reaction was 5433211000. There had been no subjective improvement in the patient, consequently treatment was discontinued for a time. At the end of two months, the patient had a shock resulting in hemiplegia.
Blood and Spinal Fluid Reactions.—The reactions obtained before intraspinal treatment, June 14, 1919, were: Wassermann reaction of the blood, negative; Wassermann reaction of the spinal fluid, negative; globulin, 0; albumin, normal; cells, 0 per cubic millimeter; colloidal gold test, 000001110. After one intraspinal injection of arsphenamized serum and four intravenous injections of arsphenamin the reactions obtained, Aug. 2, 1919, were: Wassermann reaction of the spinal fluid, not reported; globulin, +; albumin, +; cells, 13 per cubic millimeter; colloidal gold test, 555531000. After one intraspinal injection of arsphenamized serum and four intravenous injections of arsphenamin the reactions obtained, Sept. 6, 1919, were: Wassermann reaction of the spinal fluid, negative; globulin, +; albumin, +; cells, 1 per cubic millimeter; colloidal gold test, 5444321000.

Case 5.—History.—The patient was a woman, 37 years of age at the time of the first examination, who had a definite clinical picture of tabes dorsalis. For eight years she had been having sharp pains in the legs which had finally become so severe that she had to give up her work. An ataxic gait had developed, the difficulty in walking being most marked when it was dark.

Examination.—Neurologic examination showed unequal, poorly reacting pupils; absence of knee jerks and ankle jerks; ataxia in walking and a Romberg sign. The serology was interesting; a positive blood Wassermann reaction but a negative Wassermann reaction in the spinal fluid were obtained. There was a suggestion of a globulin ring by the Ross-Jones test but hardly enough to be called a definite reaction. There were 139 cells per cubic millimeter and an almost negative colloidal gold reaction, 0011230000.

Course and Treatment.—Under treatment, consisting of the injection of arsphenamin and mercury, she improved rapidly. The pains practically disappeared, and she found walking less difficult. She was enabled to return to work.

After thirty-two injections of arsphenamin and eight of mercury salicylate a second lumbar puncture was performed. The blood Wassermann reaction was negative, but the spinal fluid gave a strongly positive reaction; globulin was present; the cell count was 30 per cubic millimeter, and the colloidal gold test had become strongly positive, 5444310000.

Blood and Spinal Fluid Reactions.—The reactions obtained before treatment, Jan. 23, 1919, were: Wassermann reaction of the blood, positive; Wassermann reaction of the spinal fluid, negative; globulin, ±; albumin, ±; cells, 139 per cubic millimeter; colloidal gold test, 0011230000. After thirty-two injections of arsphenamin and eight injections of mercury the reactions obtained, Oct. 4, 1919, were: Wassermann reaction of the blood, negative; Wassermann reaction of the spinal fluid, 550000; globulin, +; albumin, +; cells, 30 per cubic millimeter; colloidal gold test, 5444310000.

Case 6.—History.—This case shows the provocative reaction in the ventricular fluid after intraventricular injections. The patient was suffering from taboparesis and was quite demented. He had acquired syphilis about nineteen years before, receiving treatment at that time. He had been deteriorat-
ing mentally for about two years before appearing at the clinic and had received a few injections of arsphenamin but was rapidly becoming worse. He was given intraventricular injections of arsphenamin serum.

**Examination.**—Examination at the time of the intraventricular injection showed unequal, irregular pupils which did not react to light but did react to accommodation; the knee jerks and ankle jerks were absent; there was a speech defect. He was depressed, memory was poor, calculating ability nil (he was a civil engineer), and he was irritable and emotionally unstable. The spinal fluid was positive in all tests.

On Dec. 15, 1919, a trephine opening was made in the calvarium by Dr. W. J. Mixter at the Massachusetts General Hospital. Fluid was withdrawn from the lateral ventricle and 15 c.c. of Swift-Ellis serum was injected. A lumbar puncture was performed at the same time. The spinal fluid was strongly positive, whereas the ventricular fluid was negative. A second ventricular fluid examination in February, 1920, was again essentially negative. On April 6, 1920, the ventricular fluid showed a relatively strong colloidal gold reaction, 4431000000; all other reactions were negative. However, on May 4, 1920, all tests had become positive, with the exception of the cell count. During this period from December, 1919, to May, 1920, the patient had received fifteen intravenous injections of arsphenamin, one intraspinal injection of arsphenaminized serum and four intraventricular injections of serum, three of which were arsphenaminized. The patient showed some clinical improvement.

In this case we would appear to have provoked positive reactions in the ventricular fluid.

**Ventricular Fluid Reactions.**—The reactions obtained, Dec. 17, 1919, before treatment, were: Wassermann reaction of the ventricular fluid, negative; globulin, 0; albumin, normal; cells, 1 per cubic millimeter; colloidal gold test, negative. After two intraventricular injections of arsphenaminized serum and eight intravenous injections of arsphenamin the reactions obtained, Feb. 20, 1920, were: Wassermann reaction of the ventricular fluid, negative; globulin, 0; albumin, normal; cells, 0 per cubic millimeter; colloidal gold test, 210000000. After one intraventricular injection of arsphenaminized serum, one intraspinal injection of arsphenaminized serum and five intravenous injections of arsphenamin the reactions obtained, April 6, 1920, were: Wassermann reaction of the ventricular fluid, negative; globulin, 0; albumin, normal; cells, 1 per cubic millimeter; colloidal gold test, 4431000000. After one intraventricular injection of arsphenaminized serum and two intravenous injections of arsphenamin the reactions obtained, May 4, 1920, were: Wassermann reaction of the ventricular fluid, 522———; globulin, 2; albumin, 2; cells, 1 per cubic millimeter; colloidal gold test, 5555320000.

These cases illustrate the fact that after antisyphilitic treatment a negative spinal fluid may become positive, or one that is slightly positive may give more strongly positive reactions.

In Case 1 the diagnosis was cleared by the effect of a provocative injection of arsphenamin. In this case the spinal fluid, which was negative prior to antisyphilitic treatment, became strongly positive in all tests after one injection of arsphenamin. It is worth while to note that the blood did not become positive. This result is also found in the other cases of this series.
Case 2 of the series shows the intensification of the spinal fluid Wassermann reaction after intravenous injection and also the provocation of a positive colloidal gold reaction, globulin and pleocytosis. It is perhaps of interest to point out in this discussion the curious fact that no provocative change was noted in the serum Wassermann reaction. In the light of present knowledge perhaps one may conclude that the patient is cured so far as visceral involvement is concerned. A latent focus of spirochetes in the nervous system was apparently activated by treatment, as was manifested by the provocative spinal fluid changes. This case is of further interest from the standpoint of conjugal neurosyphilis: paresis in the wife and latent neurosyphilis in the spouse.

The patient in Case 3 presented so definite a picture of tabes that there could be no doubt of the diagnosis, despite a spinal fluid that was negative except for a small amount of globulin and albumin increase. No provocative result occurred either in the blood or spinal fluid as the result of intravenous injection, but intraspinal subdural injections of arsphenamized serum provoked a positive Wassermann and a positive gold reaction. It is worth while to note that under treatment these reactions were reduced to almost normal. From the clinical standpoint, improvement took place even during the period in which the tests became more strongly positive. The patient, confined to bed, in the paralytic state of tabes, became able to walk without a cane, although quite ataxic.

The patient in Case 4 had undoubted tabetic disease, showing negative blood and spinal fluid reactions. Under intraspinal subdural injections the spinal fluid showed positive globulin, albumin, pleocytosis and gold reaction, but the blood and spinal fluid Wassermann tests remained negative. Contrary to the experience in Case 3, no improvement in the patient resulted from this treatment.

Case 5 is that of another patient on whom the clinical evidence made a diagnosis of tabes certain, but whose spinal fluid Wassermann reaction was negative. The blood, however, was positive, and there were 139 cells per cubic millimeter in the fluid. Under intravenous injections of arsphenamin, the Wassermann reaction in the blood serum became negative, while, on the other hand, the spinal fluid Wassermann reaction became positive. The cell count decreased, but the colloidal gold reaction became more strongly positive. From the clinical standpoint, the result of treatment was eminently satisfactory, as all pain disappeared, the ataxia became markedly improved, and the patient was able to return to work, after having been incapacitated for some months prior to treatment.
The patient in Case 6 showed the provocative results in the ventricular fluid after intraventricular injections, similar to those observed in the spinal fluid of the preceding cases.

Altman and Dreyfus\(^2\) have shown that arsphenamin may have a provocative influence on the spinal fluid in cases of primary and secondary syphilis. They examined the spinal fluid in the primary and secondary period of the disease, both before and after the intravenous administration of arsphenamin. One of their cases may be reviewed: A patient who presented no subjective or objective symptoms of nervous involvement and whose spinal fluid was negative, received 0.4 gm. arsphenamin intravenously. He then absented himself from the clinic for a period of seven weeks. When he returned, he presented a facial paralysis and an involvement of the eighth nerve. The spinal fluid at this time showed a high pleocytosis, much globulin and a positive Wassermann reaction in both high and low dilutions of the spinal fluid. The serum Wassermann reaction on both occasions was positive. These writers speak of this phenomenon as a provocative neurorecidive. A criticism of this conclusion might be offered, as it is quite possible that the condition had nothing to do with the introduction of arsphenamin, but might have occurred had it not been injected. As this occurred some time after the injection, and as there was only one injection, this case cannot be considered as strong evidence, but as illustrative of this type of reaction.

A study similar to that of Altman and Dreyfus was made by one of us (J. V. K.).\(^3\) In a series of twenty-five cases of secondary syphilis, the spinal fluid was examined before and after a course of four intravenous injections of arsphenamin, administered at intervals of seven to ten days. Provocative spinal fluid changes were observed in some of the cases on the second examination of the spinal fluid. This observation, and those of Altman and Dreyfus are in accord with the hypothesis of Gennerich,\(^4\) that arsphenamin is capable of provocative spinal fluid changes in the early period of syphilis.

The provoking of a spinal fluid by arsphenamin therapy from negative to positive is, in all probability, the expression of a Herxheimer reaction. A neurorecidive or neurorecurrence following arsphenamin injection is probably a clinical expression of this reaction. The apparent provocative reactions in the spinal fluid of neurosyphilitic patients, as herein reported, would seem to be of a similar nature and in line with the statements made above.

\(^2\) Altman and Dreyfus: München. med. Wchnschr. 60:464; 531, 1913.


PROVOCATIVE REACTION NOT FREQUENT

It should be emphasized that this provocative reaction is not a frequent occurrence even in cases in which there is evidence of central nervous system involvement with negative findings in the spinal fluid. This may be illustrated by the following cases:

CASE 7.—The patient, a man aged 36, came to the hospital after an attack of pneumonia, complaining of feeling weak. Examination showed Argyll Robertson pupils and active knee reflexes. The Wassermann reaction was positive in the blood. The spinal fluid reactions were negative. A colloidal gold test was not made at this time. The patient was given antisyphilitic treatment, which was continued for over a year. Four consecutive negative Wassermann reactions of the blood serum were then obtained. A lumbar puncture at this time was again entirely negative, except for the colloidal gold reaction, which gave a paretic type of curve, 555300000.

CASE 8.—A man, aged 35, who was brought to the hospital because of hallucinations and delusions which were apparently the result of alcoholic indulgence, had acquired syphilis a year before, for which he had been treated, and had been discharged with a negative Wassermann reaction of the blood. On admission to the hospital for his hallucinosis, he gave a negative blood Wassermann reaction and a negative spinal fluid Wassermann reaction but a pleocytosis, excess of globulin and albumin, and a paretic gold reaction. Several intravenous injections of arsphenamin were given for provocative effect, but none was found either in the blood or spinal fluid.

There appears to be some evidence that certain cases of neurosyphilis are made worse by arsphenamin therapy. This matter, which is discussed in numerous places under the heading of neurorecidive or neuroreoccurrence, has had proponents and opponents in great numbers. It seems to us, however, that there is considerable clinical evidence that occasional cases of neuroreoccurrence are caused by arsphenamin injection. This is much more frequent, probably, in the secondary period of the disease than later. The reactions to arsphenamin doubtless manifest the powerful spirochetalic action of the drug. The arsphenamin either activates foci of spirochetes or, as a result of the lysis of great masses of organisms, the toxins are liberated in large amounts, which produces pathologic results. We may then, assume that this result is expressed in a laboratory way by the appearance of provocative reactions in the blood and spinal fluid, and in a clinical way by the appearance of neurorecidives and the accentuation of symptoms.

UNFAVORABLE RESULTS OF THERAPY

The two following cases may be given as illustrations of unfavorable results of therapy:

CASE 9.—The patient was a boy, aged 9 years, with the evidence of congenital syphilis. There were three miscarriages preceding his birth. At an early age he developed snuffles and had a skin rash. The family doctor made
a diagnosis of blood disease, and he was given inunctions of mercury. At
the age of 6 he had eye trouble, which was diagnosed as interstitial keratitis.
He was given four injections of the diarsenol brand of arsphenamin, 0.15 gm.
each, in a period of six weeks. He was then given mercury by mouth. About
two weeks after the discontinuance of the arsphenamin, he sustained a left
sided paralysis.

Case 10.—A man, 49 years of age, gave a history of a genital lesion thirty­
two years previously. Twenty-five years after the lesion appeared, he began
to suffer with acute attacks of indigestion. At that time the onset of his
present symptoms began. When seen seven years after the onset of symptoms
he was having gastric crises, lancinating pains, sphincter disturbances, girdle
sensation, impotence, diplopia and impaired memory. He was given two injec­
tions of neo-arsphenamin, 0.9 gm., with a week between the injections. He
experienced a severe reaction each time. He was confined to bed for two
days after the first injection and for four weeks after the second. He was said
to be out of his mind. The pains in his legs became more severe and his speech
was affected. A year later he showed some improvement.

While many such cases could be reported, they are not usual, but
represent a small minority of all cases. Our purpose in calling attention
to them at this time is for comparison with the provocative results
shown in the spinal fluid examination of the first five cases of this
series.

Spinal Fluid Findings as an Indication for Treatment

Our intention is not to discuss the indications or contraindications
for treatment of syphilis or neurosyphilis, but rather to present in
concrete form the type of Herxheimer reaction represented by changes
in the spinal fluid. Nevertheless, a word may be said concerning the
bearing of these findings on the question of treatment. From this
standpoint, probably the most important group is that containing cases
that may be considered as latent neurosyphilis, that is, cases in which,
although there is evidence of syphilitic activity in the nervous system
as shown by the spinal fluid findings, the patient is without symptoms.
In some instances, as in the second case of our series, the spinal fluid
finding may be mild, such as a positive Wassermann reaction only.
Was harm done in this case because the reactions became stronger
after treatment? It might be stated that a continuation of treatment
produced a diminution in these findings; in Cases 3 and 5, good results
are to be accredited to treatment, despite the intensification of the
spinal fluid findings. In Cases 3 and 5 the treatment was of great
value as the patients were in better condition than they were before
treatment. Possibly some difference of opinion as to the value of
treating patients with latent neurosyphilis will depend on a theo­
retical difference of opinion. Thus, there is a school of syphilologists
who believe that syphilis is an incurable disease and that all
that therapy can be expected to accomplish is the production of a latent
condition. Another group, that may be considered as somewhat more optimistic, believes that syphilis is a curable condition, and that a great effort should be made to produce negative serology. It is quite obvious, of course, that both conceptions may be carried to a degree that is not rational. The neurologist will usually hold that the only way to prevent the occurrence of the symptoms of neurosyphilis is to treat the patients intensively before these symptoms have occurred, and it is generally held that the appearance of pathologic findings in the spinal fluid is a certain forerunner of destructive lesions. On the other hand, it would appear advisable to discontinue treatment in cases that are apparently quiescent for years and in which treatment seems to have little effect on the spinal fluid findings and which do not show any clinical improvement.

We should like to make clear, in conclusion, that these provocative changes and the cases in which, from the clinical standpoint, the condition becomes worse after treatment, are, in reality, few in number and not of sufficient frequency to cause concern.

SUMMARY

Case histories are given to show that after treatment the cerebrospinal fluid, which was negative before treatment, may become positive in all routine tests, or a weakly reacting fluid may become much stronger. This is called a provocative reaction. It may be accomplished by the intravenous or intraspinal injection of arsphenamin. This is compared to the Herxheimer reaction or the production of neurorecurrences and is considered as the laboratory analogue. The provocative reactions are shown to occur in both the ventricular and spinal fluids. This is not a frequent phenomenon, and patients with vascular neurosyphilis with negative cerebrospinal fluids may not react in this manner. However, diagnosis may occasionally be made clear in obscure cases. In none of the cases in this series was the provocative reaction obtained with the blood serum. Despite the increase in the strength of the spinal fluid reactions, clinical improvement may result, and continued treatment may again produce a negative fluid.