NONCONCOMITANCE OF SPINAL FLUID TESTS *

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TESTS APPLIED TO SPINAL FLUID IN DIAGNOSIS OF DISEASE OF CENTRAL NERVOUS SYSTEM

There are five laboratory tests commonly applied to the spinal fluid in the diagnosis of disease of the central nervous system, namely: (1) Wassermann reaction; (2) test for globulin; (3) test for increased albumin; (4) cell count (increase called pleocytosis); (5) Lange's colloidal gold test. A positive Wassermann reaction in the spinal fluid is practically specific for neurosyphilis. A positive result in the other tests, in a general way, proves a pathologic reaction of an inflammatory nature in the central nervous system. At any rate, where an inflammatory condition of the nervous system exists tests 2, 3, 4, and 5 are usually positive. In other words, in meningitis, encephalitis, tumor with meningitis sympathica, vascular insults with secondary inflammatory reaction, traumatic injury, multiple sclerosis, these four tests are generally positive. In paretic or tabetic neurosyphilis all five are usually positive.

The subject of this paper is the consideration of the relation of these tests one to the other, the identity or nonidentity of one to the other and their independent appearance and disappearance in disease conditions. There are three methods of study applicable to this problem: (*a*) chemical and biologic analysis of the substances, (*b*) review of the spinal fluids obtained from a large series of cases with attention to anomalous or unusual relations or nonrelations of findings, (*c*) frequent examination of fluids from cases of neurosyphilis undergoing treatment and in which the spinal fluid findings are influenced in the process of improvement.

WASSERMANN TEST

The Wassermann reaction in the spinal fluid is a biologic reaction pathognomonic of syphilis of the nervous system. As a rule when present it indicates an inflammatory change in the nervous system, but occasionally it is positive when the involvement is chiefly vascular, and not inflammatory. The so-called Wassermann bodies, whatever that substance is which produces deviation of complement, is an

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unknown element. There is some evidence to show that it is related to the albuminous content of the blood serum and by analogy, therefore, to the albuminous content of the spinal fluid. Thus Bruck has shown that an albumin reaction occurs in many cases giving a positive Wassermann reaction which is different from that obtained in Wassermann negative cases. Weston showed that the Wassermann producing substance does not pass through a dialyzing thimble which is impermeable to albumin. In some unpublished work at our laboratory we have shown that the addition of pure globulin to a spinal fluid giving a negative Wassermann reaction, will cause the reaction to become positive. However, these bits of evidence are far from conclusive that the Wassermann producing body is contained in the albumin and there is evidence, such as that brought forth by McDonagh, that it is a lipoid element with which the Wassermann reaction is associated. The evidence we bring in the body of this paper is against the relation of the Wassermann reaction to globulin or albumin.

It is of course evident that there is no relation between the Wassermann reaction and pleocytosis. Pleocytosis is evidence of inflammation, the Wassermann reaction of syphilis. Even where the inflammation is of syphilitic origin, the Wassermann reaction may be negative in the presence of a pleocytosis or, what is much more common, the pleocytosis may be absent with a positive Wassermann.

TEST FOR GLOBULIN

Globulin by definition is an albumin which is salted out of solution by half saturation with ammonium sulphate. Globulin does not occur normally in the spinal fluid. When present it is an evidence of pathology, and it is usually considered as proof of an inflammatory type of reaction. It also may be present, however, when there has been seepage of blood into the spinal fluid through a hemorrhage or vessel changes. If globulin is present in the spinal fluid, theoretically it means that there is an increase in the total amount of albumin, as this is an addition of an albuminous substance to the albumin normally present. As albumin which is precipitated by an acid such as trichloroacetic, is normally present in the spinal fluid in small amounts, it is increased in amount whenever globulin is present. However, it is not dependent for its increase solely on globulin, but is increased as a result of inflammation. While we have mentioned that increased globulin cannot exist without a theoretic increase in the amount of albumin, albumin can be present in increased amount without the presence of globulin. We will later show that this actually occurs. While again the globulin, albumin and pleocytosis are evidence of inflammation, it does not follow *a priori* that they are dependent one

on the other or must be present together. They are quite different elements. The same is true of the Wassermann in relation to globulin and albumin.

COLLOIDAL GOLD TEST

The chemical nature of the substance which produces the colloidal gold reaction is not clearly defined. The colloidal gold reaction is a method of differentiating albumins and was used by Lange in the endeavor to classify the type of globulin occurring in the spinal fluid. Without having succeeded in making this classification, he did discover this practical test. An obvious assumption is that the test is dependent on the albumins or globulins in the spinal fluid. It is probable that the actual type of reaction obtained is dependent to some extent on the balance of globulin and albumin present in the fluid. However, it seems to be a fact that it is not the globulin ordinarily present that causes the precipitation of the gold. Matskiewitsch attempted to identify the substance causing the colloidal gold reaction as peptone. Weston disagrees with this finding. Our clinical experience has shown that the gold reaction may be obtained with a fluid that gives no precipitation with half saturated ammonium sulphate.

Our assumption in this consideration is that these substances may appear independently one of the other, and that while on the whole they represent reaction substances of inflammation, they are in some respects entirely different responses.

SPINAL FLUID FINDINGS

Now if this be so, that these substances may occur independently one of the other (with the one exception that globulin means an increase of albumin) it would follow that a number of combinations can occur, and as a matter of fact do occur. Our evidence is derived from two sources—the routine examination of several thousand fluids and examination of spinal fluids from cases of neurosyphilis undergoing treatment.

From the first group are obtained instances of the independent appearance of the several elements and their appearance in various combinations. From the cases under treatment one finds that one test or another disappears first, and finally only one may be left positive. The different combinations appearing in these two groups are shown in the accompanying table.

Brief examples may be given of the reactions occurring in Group 1. The Wassermann reaction occurs independently of other tests, not infrequently in the endarteritic forms of cerebral syphilis. It occasionally is found as the only positive test in cases of congenital

RESULTS OF SPINAL FLUID TESTS

Spinal Fluid Finding	Condition in Which This Finding Occurred (Untreated Cases)	Findings Occurring in Treated Cases of Neurosyphilis
Pleocytosis	Congenital syphilis, undiagnosed mental disease	
Albumin	Trauma, Korsakoff's psychosis, undiagnosed mental disease	
Wassermann reaction	Vascular neurosyphilis, congenital syphilis	General paresis
Colloidal gold test	Undiagnosed condition	General paresis, tabes, etc.
Pleocytosis and albumin		
Pleocytosis and Wassermann reaction		General paresis, cerebrospinal syphilis
Pleocytosis and colloidal gold test		General paresis
Globulin and albumin	Cerebrospinal syphilis, trauma, cerebral hemorrhage, brain tumor, chronic alcoholism	General paresis
Albumin and Wassermann reaction		
Wassermann reaction and colloidal gold test		General paresis
Albumin and colloidal gold test	Undiagnosed mental disease	Cerebrospinal syphilis
Pleocytosis, globulin and albumin		
Pleocytosis, albumin, Wassermann reaction	Cerebrospinal syphilis	General paresis
Pleocytosis, albumin, colloidal gold test		
Pleocytosis, Wassermann reaction, colloidal gold test	Neurosyphilis	
Globulin, albumin and Wassermann reaction		General paresis, cerebrospinal syphilis
Globulin, albumin and colloidal gold test	Multiple sclerosis	Tabes, cerebrospinal syphilis
Albumin, Wassermann reaction and colloidal gold test		
Pleocytosis, globulin, albumin and Wassermann reaction		
Pleocytosis, albumin, colloidal gold test and Wassermann reaction		General paresis
Pleocytosis, globulin and colloidal gold test	Multiple sclerosis, brain tumor, apoplexy	General paresis
Globulin, albumin, Wassermann reaction and colloidal gold test	General paresis, cerebrospinal syphilis	General paresis
Pleocytosis, globulin, albumin, Wassermann reaction and colloidal gold test	General paresis, tabes, cerebrospinal syphilis	General paresis, tabes, etc.

syphilis, tabes and diffuse neurosyphilis. On the other hand, we have seen cases in which it was the only test to be absent. This of course is always true in nonsyphilitic inflammatory conditions giving a positive reaction for the other tests. We have also seen it even in cases of general paresis, tabes and congenital syphilis.

Pleocytosis is the most variable of the abnormal findings. It is not infrequently absent in the chronic inflammatory processes, e. g., in general paresis, tabes, brain tumor and multiple sclerosis, when the other tests are positive. On the other hand, it may be present in the absence of all other tests. For example, a woman suffering from glycosuria and a mild depression showed twelve cells per cubic millimeter; a second puncture showed sixteen cells per cubic millimeter. Her husband was a tabetic. A second example is that of a 20-year-old boy with all the signs of congenital syphilis, with outbreaks of violence, confusion and amnesia. He showed fifty-six cells per cubic millimeter, the other spinal fluid reactions being negative.

An increased amount of albumin as the only abnormal finding is not infrequent. In many instances where one finds this as the only evidence of pathology, one is at a loss to be able to interpret it, and we have seen frequent examples of this sort in dementia praecox and unclassified psychoses. According to Myerson an increased amount of albumin is common in Korsakoff's psychosis. I have been able to confirm this in a very small minority of Korsakoff cases. It also occurs after fractured skull and after fairly recent hemorrhage.

The gold reaction may occasionally be found as the only positive test, though this has been quite rare in our experience. We have found it in a few psychotic cases in which we were unable to explain its significance and in a few cases of syphilis.

It seems unnecessary to go into detail as to the combination of these findings with their clinical significance. It suffices to indicate on the table in what conditions we have found these to occur.

In cases of neurosyphilis receiving intensive antisyphilitic treatment, there usually is a change in the laboratory tests. We find that there is no general rule as to which test is the first to become weakened or to disappear, or as to which will remain positive. As one would expect, they do not all change at identically the same time. Thus in cases of general paresis undergoing treatment the Wassermann reaction is frequently unchanged despite long and intensive arsenic and mercury injections and may remain positive after all other tests have become normal. In another case with the same diagnosis and similar spinal fluid findings before treatment, the Wassermann reaction may be the first test to become negative. The same variation is to be found with the colloidal gold test, globulin and albumin.

In the table (third column) we have indicated the combination of findings that we have seen in treated neurosyphilitic cases. In addition a few examples are given in more detail.

REPORT OF CASES

OBSERVATION 1.—*Wassermann Reaction Remained Positive—All Other Tests Became Negative.*—Woman, 57 years of age, diagnosed as a case of general paresis.

Before treatment: Wassermann reaction +; globulin + + +; albumin + + +; cells 22 per c.mm.; colloidal gold test, general paresis.

After treatment: Wassermann reaction +; globulin 0; albumin negative; cells 0 per c.mm.; colloidal gold test, negative.

OBSERVATION 2.—*Colloidal Gold Test Remained Positive—All Other Tests Became Normal.*—Diagnosis: General paresis.

Before treatment: Wassermann reaction +; globulin + + +; Albumin + + +; cells 37 per c.mm.; colloidal gold test, general paresis.

After treatment: Wassermann reaction —; globulin 0; albumin negative; cells 3 per c.mm.; colloidal gold test, general paresis.

OBSERVATION 3.—*Pleocytosis and Wassermann Reaction Remained Positive; Other Tests Negative.*—The patient was a man of 35 with numerous neurasthenoid complaints, blood and spinal fluid positive to all tests. After two years of treatment spinal fluid findings were: Wassermann reaction +; globulin 0; albumin negative; cells 110 per c.mm.; colloidal gold test negative.

OBSERVATION 4.—*Globulin and Albumin Remained Positive; Other Tests Negative.*—Diagnosis: General paresis.

Before treatment: Wassermann reaction +; globulin + + +; albumin + + +; cells 90 per c.mm.; colloidal gold test 5 5 5 5 5 3 0 0 0.

After treatment: Wassermann reaction —; globulin + +; albumin + +; cells 3 per c.mm.; colloidal gold test negative.

OBSERVATION 5.—*Colloidal Gold Test and Wassermann Reaction Remained Positive; Other Tests Became Negative.*—Diagnosis: General paresis.

Before treatment: Wassermann reaction +; globulin + + +; albumin + + +; cells 22 per c.mm.; colloidal gold test, general paresis.

After treatment: Wassermann reaction +; globulin 0; albumin negative; cells 0 per c.mm.; colloidal gold test, general paresis.

OBSERVATION 6.—*Albumin and Colloidal Gold Test Remained Positive; Other Tests Became Negative.*—Diagnosis: Cerebrospinal syphilis.

Before treatment: Wassermann reaction +; globulin + + +; albumin + + +; cells 11 per c.mm.; colloidal gold test 5 4 3 2 2 1 0 0 0 0.

After treatment: Wassermann reaction negative; globulin 0; albumin +; cells 3 per c.mm.; colloidal gold test 0 1 3 4 3 1 0 0 0 0.

OBSERVATION 7.—*Globulin, Albumin and Wassermann Reaction Remained Positive—Pleocytosis and Colloidal Gold Test Became Negative.*—Diagnosis: General paresis.

Before treatment: Wassermann reaction +; globulin + + +; albumin + + +; cells 45 per c.mm.; colloidal gold test 5 5 5 5 5 5 2 0 0.

After treatment: Wassermann reaction +; globulin + +; albumin + +; cells 4 per c.mm.; colloidal gold test negative.

OBSERVATION 8.—*Globulin, Albumin and Colloidal Gold Test Remained Positive—Wassermann Reaction and Pleocytosis Became Negative.—Diagnosis: Cerebrospinal syphilis.*

Before treatment: Wassermann reaction +; globulin + + +; albumin + + +; cells 56 per c.mm.; colloidal gold test, 0 0 1 3 3 2 1 0 0 0.

After treatment: Wassermann reaction negative, globulin +; albumin +; cells 0 per c.mm.; colloidal gold test 2 2 2 3 3 1 0 0 0 0.

OBSERVATION 9.—*Wassermann Reaction Became Negative; Other Tests Remained Positive.—Diagnosis: Cerebrospinal syphilis.*

Before treatment: Wassermann reaction +; globulin + + +; albumin + + + +; cells 41 per c.mm.; colloidal gold test, general paresis.

After treatment: Wassermann reaction —, globulin + +; albumin + +; cells 9 per c.mm.; colloidal gold test, syphilitic.

OBSERVATION 10.—*Pleocytosis Reduced to Normal; Other Tests Remained Negative.—This is a very frequent finding.*

Even though not a part of this discussion, we would like to add that the Wassermann reaction in the blood serum varies independently of the spinal fluid findings. Thus it may become negative while all the spinal fluid tests remain unchanged or it may remain positive when all the spinal fluid tests become negative. It is also pertinent to note that the changes in these spinal fluid tests do not always parallel clinical changes in the patients. Thus we have seen illustrations where although the tests became negative the symptoms were in no way improved; and on the other hand, where there was marked symptomatic improvement without any change in the tests.

SUMMARY

Of the five spinal fluid laboratory tests commonly used, only cells and albumin are normal constituents of the fluid, and the excess amounts of these are evidence of pathology. The Wassermann reaction is for practical purposes specific for syphilis of the nervous system. Pleocytosis, globulin, albumin and colloidal gold reaction are generally indicative of an inflammatory reaction of brain, cord or meninges. These tests may be positive owing to infection, mechanical injury, tumor, trauma, vascular insults, multiple sclerosis, etc. As a rule, globulin, albumin increase, pleocytosis and a positive colloidal gold reaction occur together and when the Wassermann reaction is positive, it is usual for the other four to be positive also. Although usually present together and in a general way indicative of the same pathologic condition, each reaction is produced by a distinct chemical element which may be present alone (except that theoretically globulin means an increase in the total amount of albumin, as globulin is a special albumin). Thus one may find the Wasserman reaction positive, all other tests negative, a positive colloidal gold reaction as the only positive finding, only a pleocytosis or merely an albumin increase.

Further, they may occur in various combinations. This is theoretically possible on the basis of difference in chemical constitution, and it is shown in this paper that this actually does occur.

Additional evidence of the independence of each element is offered in the result of treatment of cases of neurosyphilis. Starting with all tests positive, it is shown that they become negative often one at a time and the different combinations are left positive, or only one is left positive.

CONCLUSIONS

1. There is a nonconcomitancy of the inflammatory elements of the spinal fluid commonly tested for in diagnosis of disease of the central nervous system.

2. Any one may be present or absent when the others are present—with the exception that globulin presages an increased amount of albumin.

3. No spinal fluid can be considered negative in which all these tests have not been used.

4. No one element tested for contains the element or fraction that gives another test, except that the total albumin contains the globulin fraction, in part at least.

5. In neurosyphilitic cases receiving treatment these substances disappear at differing rates which vary in different cases, so that no general law can be laid down as to which element is most easily affected by treatment in any particular case, though in general the pleocytosis disappears first.

6. The presence or absence of these products of inflammatory reaction does not always parallel the clinical change in the treated neurosyphilitic patient.