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THE BUTYRIC ACID TEST FOR SYPHILIS IN THE
DIAGNOSIS OF METASYPHILITIC AND
OTHER NERVOUS DISORDERS.¹

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General paralysis, although in its clinical aspects a disease that can be frequently diagnosed almost at a glance, is often simulated so closely by other disorders and has so many imitators among the psychoses produced by alcohol, vascular lesions and other causes, that various tests have been devised in recent years for its more certain detection. This paper will be devoted to a consideration of the butyric acid reaction (Noguchi) in relation to the diagnosis of syphilitic affections of the central nervous system, in which class of diseases general paralysis is included.

We have subjected the cerebro-spinal fluid from a series of cases of general paralysis, tabes, cerebral and spinal syphilis and some other mental diseases to this test² and at the same time to the complement-fixation test of Wassermann³ and to cyto-diagnosis according to the method of Ravaut.⁴

¹ Received for publication March 15, 1909.

² Noguchi, *Jour. of Exper. Med.*, 1909, xi, 84; *Proc. of the Soc. for Exper. Biol. and Med.*, 1909, vi, 51.

³ Wassermann and Plaut, *Deutsche med. Woch.*, 1906, xxxii, 1937.

⁴ Ravaut, *Ann. de dermat. et de syph.*, 1903, iv, 537.

THE BUTYRIC ACID TEST.

The cerebro-spinal fluid of syphilitic individuals contains, as does the blood serum, a higher content of globulin and especially of euglobulin than normal cerebro-spinal fluid. It is this increase that makes the butyric acid test applicable to the diagnosis of syphilis.

The mode of applying the test is as follows: one or two parts⁵ of spinal fluid⁶ are mixed with five parts⁷ of 10 per cent. butyric acid solution⁸ and are heated over a flame to a brief boiling. One part⁹ of normal solution of sodium hydroxide is then added quickly to the heated mixture and the whole is boiled once more for a few seconds. The presence of an increased content of protein in the spinal fluid is indicated by the appearance of a granular or flocculent precipitate which gradually settles under a clear supernatant liquid. The intensity of the reaction varies greatly according to the amount of protein which a given specimen contains, but the granular appearance of the precipitate means a positive reaction for syphilis or para-syphilitic affections.

With normal or non-specific specimens there will be a slight opalescence or sometimes a marked turbidity which, however, does not settle out in several hours or even in twenty-four hours.

The test was applied in this manner to all the samples of cerebro-spinal fluid examined and, at the same time, portions of the samples were tested by means of the Wassermann syphilis test which being now established as indicating syphilitic infection in a high percentage of cases with definite histories must be accepted as giving trustworthy results in cases in which definite histories are not obtainable. In some instances the modification of the Wassermann test introduced by one of us¹⁰ (Noguchi) was used in place of the original method.

The cytological examination, which was the second form of control employed, was that of Ravaut, but with one point of difference,

⁵ 0.1 or 0.2 c.c. are sufficient and convenient.

⁶ Must not contain blood.

⁷ 0.5 c.c. for the quantities above specified.

⁸ Best in 0.9 per cent. salt solution.

⁹ Namely, 0.1 c.c. in this case.

¹⁰ Noguchi, *Jour. of Exper. Med.*, 1909, xi, 392.

as stated, namely, the use of Ehrlich's triacid stain, which was found very satisfactory. In most of the cases two or more such examinations of the cerebro-spinal fluid were conducted at intervals. It is important to note that in no case did the results of the different examinations vary essentially. The rule adopted by us for the cyto-diagnosis was to regard less than ten cells to a field of the microscope given by a one-sixth lens as negative, more than twelve cells as positive, and ten, eleven and twelve cells to such a field as doubtful. The drop employed came within the limits of a one-third inch objective; but experience enables one to make an accurate calculation even when the drop is less uniform in size or has changed by evaporation. The presence of a small number of red corpuscles does not prevent accurate estimation of the white cells. The modification of the cytological method introduced by Alzheimer¹¹ was employed in a number of instances but without practical advantages.¹²

Since Nonne and Apelt¹³ had already observed an increase in the protein fraction, probably consisting of globulin, in the cerebro-spinal fluid of general paralytics, constituting their so-called "phase I," we applied their method to a large number of cases but with very unsatisfactory results. The poor definition obtained between positive and negative readings made the deduction difficult and questionable.

RESULTS IN WHICH THE DIAGNOSIS WAS REASONABLY CERTAIN.

In Table I we have brought together our results in 126 cases whose diagnoses could be made reasonably certain from the symptoms. In a part of the cases the diagnosis was confirmed subsequently by autopsies.

The table brings together the results of the three tests mentioned on several classes of syphilitic affections and on a smaller number of cases of nervous affections in which a syphilitic element could be excluded with a high degree of positiveness. A comparison shows immediately that there is a close correspondence in the results

¹¹ Alzheimer, *Centralbl. f. Nerven- und Psychiat.*, 1907, xxx, 449.

¹² The cytological study has been carried out by Dr. Moore at the Pathological Institute of the State Hospitals.

¹³ Nonne and Apelt, *Arch. f. Psychiat.*, 1907-8, xliii, 433.

TABLE I.

Results in Cases in Which the Diagnosis Was Reasonably Certain.

Cases.	No. of cases.	Butyric acid reaction.			Wassermann reaction.			Cell count.		
		+	-	±	+	-	±	+	-	±
Syphilis										
Secondary stage (without nervous symptoms)	3	3	0	0	0	3	0	0	3	0
Tertiary stage (without nervous symptoms)	1	1	0	0	0	1	0	0	1	0
Cerebral syphilis	3	3	0	0	1	1	1	3	0	0
Spinal syphilis	3	3	0	0	2	1	0	3	0	0
Hereditary syphilis	10	9	0	1	8	2	0			
Metasyphilis										
general paralysis										
cerebral	43	37	4	2	32	6	5	39	2	2
tabetic	17	17	0	0	12	3	2	16	1	0
Tabes	11	11	0	0	6	4	1	11	0	0
	91	84	4	3	61	21	9	72	7	2
Psychoses										
Arterio-sclerotic	3	1	2	0	1	2	0	1	2	0
Traumatic	2	0	2	0	0	2	0	0	2	0
Senile	1	0	1	0	0	1	0	0	1	0
Epileptic	6	0	6	0	0	5	1	0	6	0
Alcoholic	7	0	6	1	3	3	1	0	6	1
Manic-depressive	2	0	2	0	1	1	0	0	2	0
Dementia precox	11	1	10	0	1	8	2	1	10	0
Imbecility	2	0	2	0	0	2	0	0	2	0
	34	2	31	1	6	24	4	2	31	1

obtained. On closer inspection the results of the butyric acid reaction are found to agree more nearly with those of cytodagnosis than does the Wassermann test. The explanation for this may reside in the fact that there sometimes occurs in the cerebro-spinal fluid, as in the blood-serum, substances which are antihemolytic and which, therefore, inhibit hemolysis even when all antigen has been omitted from the mixtures. When the attempt is made to eliminate the action of the antihemolysis by diminishing the quantity of cerebro-spinal fluid in the mixtures, a doubtful reaction may result because of too great dilution of the substances acting as antibody.

It is to be regretted that the number of cases of secondary and tertiary stages is so small. The explanation for this fact is to be found in the difficulty of securing the consent of patients not suffer-

ing from nervous affections to submit to lumbar puncture. The results obtained in the four cases are, however, instructive. It will be observed that all four gave the butyric acid reaction and were negative to the Wassermann test and to cytodagnosis. The explanation of the discrepancy is probably as follows: in active, secondary and tertiary syphilis the increase in globulin of the blood plasma affects also the cerebro-spinal fluid, but the absence of specific lesions of syphilis in the central nervous system determines that the cells are not increased and the antibody on which Wassermann's test depends is not produced *in loco* and does not pass with the fluid in sufficient amount from the blood to give the reaction. Moreover, the discrepancy also indicates that there is no necessary relation between the globulin-content and the Wassermann test. The three cases of cerebral syphilis gave positive results with the butyric acid test and cytodagnosis but remained doubtful to the Wassermann test.

The most striking results are given by the cases of general paralysis of which more than 90 per cent. reacted positively. The cases of the tabetic forms of general paralysis and of simple tabes all gave positive reactions. The close agreement between the butyric acid reaction and cytodagnosis is in contradistinction to the discrepancy between the latter and the Wassermann test.

AN ANALYSIS OF THE RESULTS FROM THE STANDPOINT OF SYPHILIS.

In order to study the reactions in relation to metasyphilitic affections, we shall omit those cases with obvious active symptoms of syphilis and disregard all cases in which a reliable history is lacking and the physical examination was insufficient to establish the existence of a previous syphilitic infection. As the majority of the cases comprising our material were derived from an hospital for the insane, only a comparatively small number lend themselves to this consideration. Fifty-nine cases are available for analysis.

Those classed as syphilis + are cases with good histories or unmistakable signs of syphilis or both. Those classed as syphilis — gave intelligent statements, denied the disease and no indication of it could be found.

The results show that cases of general paralysis and tabes with definite histories of a syphilitic infection in early life all yield posi-

TABLE II.

Analysis of the Reactions With Regard to Syphilis.

Cases.	No. of cases.	Butyric acid reaction.			Wassermann reaction.			Cell count.		
		+	-	±	+	-	±	+	-	±
General paralysis and tabes										
Syphilis +	36	34	1	1	26	8	2	36	0	0
Syphilis -	16	12	3	1	10	3	3	11	3	2
Other diseases										
Syphilis +	1	1	0	0	1	0	0	1	0	0
Syphilis -	12	1	11	0	3	8	1	1	11	0

tive reactions to all the tests in a very high percentage, amounting to 100 per cent. for cytodagnosis, 94 per cent. for the butyric acid test and 72 per cent. for the Wassermann test. It is noteworthy, however, that the same class of diseases affecting individuals without previous histories of a syphilitic infection also give a high, though somewhat lower percentage than the first group. For the butyric acid test, which was the highest, the percentage was 75, for the cell count it was 60 and for the Wassermann test 62.5.

The clinical features of these two groups of cases, namely, the one with definite syphilitic histories and the other without, were not different in any way; moreover, the severity of the symptoms does not always run parallel with the intensity of the reactions. There existed, however, a rough parallelism between the increase of cells and the strength of the butyric acid reaction.

With the cases which were neither paralytic nor tabetic, the results were entirely different. A case of dementia precox with a reliable history of a previous syphilitic infection gave positive reaction to all the tests.

Twelve cases without histories of syphilitic infection were examined with the result that one gave positive reaction to all the tests and two others reacted positively only to the Wassermann, but not to the other two tests. All cases of dementia precox constituting this group reacted negatively to all the tests.

It may be recalled here that Raviart, Breton and Petit¹⁴ obtained about 27 per cent. of positive reactions with the Wassermann test using the blood of cases suffering from dementia precox.

¹⁴ Raviart, Breton and Petit, *Rev. de Méd.*, 1908, xxviii, 840.

THE BUTYRIC ACID TEST AND POST-MORTEM FINDINGS.

In all, seventeen cases of the series have come to autopsy. Fifteen had given positive findings with the butyric acid test, fourteen being diagnosed as general paralysis and one as cerebral syphilis. Two had given negative results with the acid. The autopsy findings and the results of the test agreed in every case.

In a number of cases the results of the examination of the cerebro-spinal fluid has been the means of establishing an otherwise doubtful diagnosis or of correcting an erroneous one. This is true of cases giving negative as well as positive reactions. In how far this result will be more generally applicable to diagnosis, only a wide series of observations can decide. The outlook seems extremely hopeful.

THE BUTYRIC REACTION IN GENERAL DISEASES.

It would appear that the butyric acid reaction will come to serve a useful purpose in psychiatric diagnosis. This is the opinion of Mott¹⁵ also, who has already expressed his opinion. It is, however, necessary that the limitation of its applicability should be precisely defined by subjecting the cerebro-spinal fluid from other general diseases to the test. Such a wide examination can alone determine whether the reaction is specific for syphilitic lesions, which at the outset seemed doubtful, or whether the changes in the globulin concentration of the cerebro-spinal fluid occurred in many other diseases than syphilis. It could be predicted, of course, that in all conditions of acute exudative inflammations of the cerebro-spinal meninges, the reaction would be obtained. The change in the character of the fluid and the increase in blood proteins predetermined this result. Table III shows that in all acute inflammatory conditions of the cerebro-spinal meninges the reaction is positive. There is, however, no difficulty whatever in making a diagnosis in this class of cases and they do not, therefore, come into account. The precipitate given with butyric acid is very heavy as would be expected. Even with tubercular meningitis the symptoms and other criteria easily differentiate that condition from syphilitic or meta-syphilitic ones. The cases of hydrocephalus are a little more con-

¹⁵ Mott, *British Med. Jour.*, 1909, i, 454.

fusing, but as only two came under observation and one gave the Wassermann test also, the existence of congenital syphilis should be thought of. The general diseases, among which are typhoid fever and pneumonia, with which meningeal implication may be absent are not attended by changes in the cerebro-spinal fluid that lead to the butyric acid reaction.

TABLE III.
The Butyric Acid Reaction in General Diseases.

Cases.	No. of cases.	Butyric acid reaction.			Wassermann reaction.		
		+	-	±	+	-	±
Diseases of the meninges							
Epidemic cerebro-spinal meningitis	14	14	0	0	0	14	0
Pneumococcal meningitis	6	6	0	0	0	6	0
Influenzal " "	1	1	0	0	0	1	0
Tubercular " "	30	30	0	0	0	30	0
Hydrocephalus externus	2	2	0	0	1	1	0
	53	53	0	0	1	52	0
Diseases without meningeal involvement							
Typhoid fever	1	0	1	0	0	1	0
Pneumonia	4	0	4	0	0	4	0
Pulmonary tuberculosis	1	0	1	0	0	1	0
Enterocolitis	2	0	2	0	0	2	0
Rachitis	1	0	1	0	0	1	0
Uremia	2	0	2	0	0	2	0
Septicemia	1	0	1	0	0	1	0
Miscellaneous without nervous involvement	12	0	11	1	0	10	2
	24	0	23	1	0	22	2

On the basis of these tests, we consider that the butyric acid reaction suffices to distinguish normal from pathological cerebro-spinal fluid and especially from that fluid which has been altered through an increase in its protein constituent. We would, therefore, point out that by its means it may be possible to determine the limits of some ill-defined inflammatory conditions of the meninges, such as, for example, the so-called meningitis serosa, in which condition microorganisms have not yet been demonstrated satisfactorily and the cellular exudations are absent, and yet abnormal serous exudations seem to occur. If these exudations contain an excess of protein constituents as compared with the normal transudate the differ-

ence should be appreciable by this test. Moreover, whether this increase is due to or attended by syphilis could be determined by the Wassermann test or the modification of it recommended by one of us (Noguchi).

We believe, moreover, that in tubercular meningitis the butyric acid reaction will always be positive. In a suspected case, therefore, in which no tubercle bacilli have been found and the tuberculin reaction is unconvincing, this test, if negative, would have diagnostic value. We have applied the test to a small number of doubtful cases of suspected tubercular meningitis. Those giving negative results subsequently proved not to be tubercular.

SUMMARY.

1. In the secondary and tertiary stages of syphilis without direct involvement of the nervous system the cerebro-spinal fluid yielded the butyric acid reaction of feeble intensity. The fluid under these conditions gave neither a positive cytodiagnosis nor the Wassermann test for syphilis.
2. The cerebro-spinal fluid of cases of hereditary syphilis showed a positive butyric reaction in about 90 per cent. and a positive Wassermann test in about 80 per cent. of the cases examined.
3. The cerebro-spinal fluid of cases of cerebral and spinal syphilis yielded the butyric acid reaction and the cytodiagnosis in every instance (100 per cent.) and gave the Wassermann reaction in from 50 to 75 per cent. of those examined.
4. The cerebro-spinal fluid from cases of general paralysis gave positive butyric acid reactions in 90 per cent., positive cell counts in 91 per cent., and positive Wassermann test in 73 per cent. of those examined.
5. The cerebro-spinal fluid from cases of tabes dorsalis gave positive butyric acid reactions and cell counts in 100 per cent. and positive Wassermann test in 53 per cent. of those examined.
6. The cerebro-spinal fluid from other forms of psychosis in which a syphilitic history was not obtained gave positive butyric acid reactions and cell count in 2.8 per cent. and Wassermann test in 13 per cent. of those examined.

7. The cerebro-spinal fluid from cases of acute inflammatory diseases of the meninges always gave a flocculent precipitate with the butyric acid reaction but never gave the Wassermann test.

8. The cerebro-spinal fluid from persons suffering from typhoid fever, pneumonia, pulmonary tuberculosis, etc., in which the meninges are not inflamed, gave neither the butyric acid nor the Wassermann test.

9. We think it justifiable to conclude that the butyric acid reaction affords a ready means of distinguishing normal from pathological cerebro-spinal fluid and will prove to be useful in routine clinical practice, especially in detecting syphilitic disease and in confirming or setting aside certain doubtful diagnoses of syphilitic or metasyphilitic lesions of the central nervous system. The reaction should commend itself as a valuable addition to the Wassermann test, the results of which it is capable of confirming and extending.