

USE OF A MODIFIED TAKATA REACTION IN THE EXAMINATION OF THE CEREBROSPINAL FLUID OF CERTAIN PSYCHOSES.

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THE Takata reaction has hitherto been mainly applied as a serum protein test and has been claimed useful in the diagnosis of liver disease.

It has been modified and applied to the cerebrospinal fluid (Takata-Ara (1)). Preliminary investigators found positive results in syphilis of the central nervous system, and it was thought to be a characteristic of this condition. Subsequent workers, however, found that organic conditions other than neuro-syphilis produced similar positive reactions, with the result that the test fell somewhat into disrepute. Now, however, it seems to be established that the test is indicative of a change in the albumin-globulin (euglobulin) ratios in the cerebrospinal fluid. This condition is mainly found in syphilis of the central nervous system, but occurs, of course, in other conditions affecting the central nervous system, especially where degenerative processes are involved.

In 1938 the author (2), described the use of a modified Takata reaction in testing the cerebrospinal fluid of cases of organic psychoses, mainly dementia paralytica. That preliminary investigation apparently confirmed the hypothesis that the Takata reaction arises from a disturbance of the albumin-globulin ratio of the cerebrospinal fluid.

The present paper illustrates an endeavour to obtain diagnostic criteria from the application of the modified reaction to specimens of cerebrospinal fluid taken from more varied clinical material. Of the cases examined one half suffered from neuroses or psychoses of types which are not generally considered to be connected with organic processes in the brain. The high degree of sensitivity of the Takata reaction was thought to be of use in detecting minute changes in the protein composition of the cerebrospinal fluid.

TECHNIQUE.

One would naturally expect that cerebrospinal fluid taken from such "non-organic" cases would have a small total protein content, and the estimation would call for a greater degree of accuracy than were the test to be applied to cases of the organic type such as described in the first paper. In the first paper attention was focussed on the time factor in performing the test. In this series still greater attention was paid to this point. A somewhat different method of reading the results was formulated and the appearance of the turbidity was listed in the following categories:

- (a) Any turbidity appearing within the first 8 minutes of the test.
- (b) Any turbidity appearing after a lapse of 8 minutes.
- (c) Definite turbidity making its appearance after a lapse of 30 minutes.

It was noted that even slight variations in temperature had a marked effect on the time of appearance of turbidity. A constant temperature of 15° C. will be found to be the optimum for the conditions described in this paper. Failing these conditions, allowances with regard to the time factor have to be made. For example an increase in the temperature of 10° C. above the "optimum" will reduce the reaction time to a very considerable extent.

REAGENTS.

1. 0.36 per cent. aqueous solution of anhydrous sodium carbonate.
2. 0.5 per cent. aqueous solution of mercuric chloride.

In the original paper it was stressed that the reagents were satisfactory if equal volumes of the reagents gave a faint pink colour on the addition of phenolphthalein.

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It is now preferred to add 0.1 c.c. of each of the reagents to 1 c.c. of distilled water and then add one drop of phenolphthalein. By this method the precipitation of a double salt is avoided—a condition which arose when the former method of testing the reagents was employed.

TEST.

To 1 c.c. of fresh cerebrospinal fluid add 0.1 c.c. of the sodium carbonate solution. Mix well and add 0.1 c.c. of the mercuric chloride solution and again mix well and allow to stand.

READING.

1. The tube is inspected at frequent intervals during the first 8 minutes, the appearance of any turbidity being noted.

2. Readings are then made at intervals of 5 minutes until 30 minutes have elapsed.

In the majority of cases the turbidity will commence during the first few minutes, but in others the reaction will not occur until later. The turbidity may or may not increase as time elapses and the time of the first appearance of turbidity should be noted. Any turbidity occurring after the first 8 minutes was prefixed by the word "late." The degree of turbidity at the end of 30 minutes was noted as the result.

Hence the 30-minute reading made in a reaction which commences during the first 8 minutes will be :

Strong positive (+ +), positive (+), weak positive (W +), Trace (Tr.), or Faint Trace (F.Tr.), and ± (doubtful).

But in a case where the reaction does not commence during the first 8 minutes it will be :

Late strong positive (L. + +), late positive (L. +), etc.

3. Very occasionally a definite reaction will commence after 30 minutes, and all tubes which give a negative reading at the end of 30 minutes should be allowed to stand until 90 minutes have elapsed to exclude these very late positive results.

Daylight was used for reading and the turbidity made evident by holding the tube against a dark background in front of a window. In very dull daylight readings were made by holding the tube in the light from a microscope lamp against a dark background, although this method tends to magnify the strength of the reaction.

As might be expected, many cases in the series might yield only very weak results, and to render the results impartial at least two observers and sometimes three or four have read the tubes independently, and completely unaware of the clinical diagnosis.

Cerebrospinal fluid is usually collected in two or more portions, and the fluid taken for the reaction was wherever possible taken from the second fraction to avoid admixture with blood. In every case the following was also adopted as the routine examination :

1. *Cells*.—A Fuchs-Rosenthal chamber was used and 3 cmm. were counted, the result being expressed as Cells/3. Fluids containing over 1500/3 red cells were omitted. Fluids containing more than 200/3 red cells have been marked in the tables.

2. *Pandy*.—Six drops of a saturated aqueous solution of phenol were placed in a watch glass and one drop of fluid was allowed to run down the glass and into the phenol. The glass was not agitated and no significance was attached to a reaction occurring after 10 seconds.

3. *Nonne*.—The "ring test" modification was used. 0.5 c.c. of fluid was placed in a test tube, and with the tube at an angle, 0.5 c.c. of saturated ammonium sulphate solution was allowed to run down the tube and through the fluid. The reaction should not be read before 3 minutes. Reactions occurring after 10 minutes were called "late," and discarded when they occurred later than 20 minutes. The result of the reaction was read with the help of a hand lens.

4. *Wassermann and Meinicke*.

5. Lange and total protein estimations have been carried out in a number

of cases (one of the usual turbidometric methods being used for the protein estimation). As it is known that these tests do not assist in the diagnosis of non-organic psychoses, the results have been omitted.

CASE MATERIAL AND RESULTS.

1. Syphilis and neuro-syphilis (25 cases).
2. Non-psychotic organic neurological cases (24 cases).
3. Psychoses due to senile dementia, arteriosclerosis, and other more generalized organic conditions (12 cases).
4. Involutional psychoses (10 cases).
5. Hysteria and neurotic conditions (7 cases).
6. Manic and depressive states (8 cases).
7. Schizophrenia (53 cases).
8. Schizophrenic states superimposed on cerebral disease (7 cases).
9. Atypical psychoses (14 cases).
10. Psychoses with disputed diagnoses (5 cases).

1. Syphilis and Neuro-syphilis.

The results were in conformity with those published in the previous paper. It is of interest to note that in some cases of congenital syphilis the Takata reaction was weakly positive with the other reactions being negative. In some cases the clinical diagnosis could not be confirmed by any of the reactions, including Wassermann and Lange.

2. Non-psychotic Organic Neurological Cases.

Among these a great variety of different organic disorders of the nervous system were present. In 10 of these cases all three reactions were positive, although to varying degrees. In 1 case a late weak positive Takata was present with a doubtful Pandy reaction. In 6 cases a weak positive Takata reaction occurred with doubtful or very weak Nonne reactions. In 7 cases the Takata reaction varied from faint trace to weak positive, the Pandy and Nonne reactions being negative. These cases were (a) post-traumatic condition, (b) recovering cerebrospinal meningitis, (c) hemiplegia of long standing, (d) encephalitis following vaccination, (e) case of epilepsy, (f) suspected brain tumour, (g) case of sciatica.

It is interesting to note that in one case of commencing cerebrospinal meningitis Pandy and Nonne reactions were strongly positive while the modified Takata reaction was very late positive.

In the following tables the abbreviations used are :

1. For reactions commencing during the first few minutes : \pm (doubtful), F.Tr. (faint trace), Tr. (trace), W.+ (weak positive), + (positive), ++ (strong positive).

2. For reactions commencing after 8 minutes : L (late) prefixes the readings which are identical with those above.

3. Psychoses due to Senile Dementia, Arteriosclerosis and other more generalized Organic Conditions.

Pandy.	Nonne.	Takata.	Cases.	Clinical remarks, etc.
—	—	—	1	Schizoid psychosis. Pupils show no reaction to light. Babinski and other pyramidal symptoms positive. W.R. negative. Cells 12/3.
—	—	—	1	Froehlich syndrome.
—	—	\pm	1	Senile dementia.
—	—	L.Tr.	1	Korsakoff syndrome.
—	\pm	\pm	1	Senile dementia.
—	Tr.	\pm	1	Organic psychosis.
—	W.+	L. \pm	1	Puerperal psychosis.
\pm	Tr.	Tr.	1	Depressive psychosis plus pernicious anaemia.
Tr.	Tr.	L.Tr.	1	Hypovitaminosis.
Tr.	L.Tr.	L.Tr.	1	Arteriosclerosis.
W.+	Tr.	—	1	"Organic" psychosis.
Tr.	W.+	W.+	1	Arteriosclerotic dementia.
Total, 12 cases.				

In only two of these cases were all reactions negative. The case of Froehlich's syndrome did not show any sign of central nervous neurological disturbance. The other case had remained stationary for a considerable time. In the remainder of the cases the strength of the reactions ran almost parallel to the clinical condition.

4. Involutional Psychoses.

TABLE A.—Cases not complicated by Organic Factors.

Pandy.	Nonne.	Takata.	Cases.	Clinical remarks, etc.
—	—	—	1	Typical involutional melancholia, feelings of guilt, no projected delusions, hypertension.
—	—	L. ±	1	Mild paranoid depressive delusions.

TABLE B.—Cases complicated by Organic Factors.

Pandy.	Nonne.	Takata.	Cases.	Clinical remarks, etc.
—	—	L.Tr.	1	Plus organic symptoms after electro-shock therapy.
—	L.Tr. or stronger	L. ± or stronger	3	Typical depression with feelings of guilt, but complicated by symptoms indicative of organic cerebral disorder.
—	±	+	1	Depressive paranoid delusions and hallucinations. Slight reflex differences.
—	Tr.	Tr.	1	Pyramidal signs due to arteriosclerosis cerebri.
—	±	L. +	1	Ditto.
±	—	Tr.	1	Plus mild organic dementia.

Total, 10 cases.

It appears to be significant that while in the two uncomplicated cases Nonne and Pandy were both negative, and in one case the Takata was late doubtful, the other being negative, the findings were different in the complicated cases. In the cases complicated by organic factors, the Takata results, with one exception, were accompanied by positive Nonne or Pandy reactions in varying degrees of positivity.

5. Hysteria and Neurotic Conditions.

Pandy.	Nonne.	Takata.	Cases.	Clinical remarks, etc.
—	—	—	4	Hysteria.
—	—	L. ±	1	Schizoid personality.
—	—	L.F.Tr.	1	Severe conversion hysteria with strong tremor of seven years' standing.
—	±	—	1	Hysteria superimposed on slight cerebral disorder. Cells 9/3.

Total, 7 cases. Average cell count $1\frac{1}{3}$, if last case is omitted.

The organic component in the last case is expressed by the doubtful Nonne reaction and an increased cell count. The very low average cell count ($1\frac{1}{3}$), if the organic case is omitted, is remarkable. An evaluation of the very weak and late Takata reactions in cases with very severe neuroses of long standing will not be possible until more material is available.

6. Manic and Depressive States.

Pandy.	Nonne.	Takata.	Cases.	Clinical remarks, etc.
—	—	—	6	—
—	—	L. ±	1	Old head injury.
—	—	L.Tr.	1	Pyramidal disturbances caused by electro-shock therapy (?).

Total, 8 cases. Average cell count $2\frac{2}{3}$.

This group showed entirely negative results in six cases, a "late doubtful" and "late trace" reaction in two cases, both complicated by organic features. The average cell count was 2.5/3. One of the "negative" cases, which appeared to be typically manic when the cerebrospinal fluid was examined, developed a "toxic" psychosis later on. Two more of these negative cases had suffered severe head injuries one and two years respectively before the outbreak of the psychosis.

7. Schizophrenia.

TABLE A.—*Typical Clinical Cases with "Characteristic" Reactions in the Cerebrospinal Fluid.*

Pandy.	Nonne.	Takata.	Cases.	Clinical remarks, etc.
—	—	Tr. or W. +	28	Two acute cases with 15/3 and 8/3 cells respectively and two cases with about 1500/3 red cells.
—	±	Do.	11	—
±	—	"	3	—
±	±	"	7	Including 2 cases with 900/3 and 1500/3 red cells respectively.
Total, 49 cases.				Average cell count 5/3.

TABLE B.—*Cases with Less Characteristic Reactions.*

Pandy.	Nonne.	Takata.	Cases.	Clinical remarks, etc.
—	—	—	1	Typical schizophrenic behaviour, but without paralogia and psycho-motor symptoms. Some manic-depressive features. Heredity: Mother, melancholia; sister, epilepsy and mental deficiency.
—	—	L. ±	1	Recovering after electro-shock therapy.
—	±	F.Tr.	1	Beginning schizophrenia.
±	Tr.	W. +	1	Schizophrenia with long-standing hypertension.
Total, 4 cases.				Average cell count 5/3.

The cases in Table A are apparently characterized by "trace" or "weak positive" Takata reactions, the other reactions being negative or doubtful.

In Table B the reactions were different from those of Table A, the Takata reaction being either negative or weaker or "late" or connected with a slightly stronger Nonne.

8. Schizophrenic States Superimposed on Cerebral Disease.

Pandy.	Nonne.	Takata.	Cases.	Clinical remarks, etc.
—	—	Tr. or stronger	3	1 chorea, 1 mental deficient, 1 chronic alcoholism.
—	—	L.Tr.	1	Pernicious anaemia.
—	±	F.Tr.	1	Mental deficient.
—	W. +	+	1	"Organic" disease of the brain.
+	+	++	1	Hereditary paraplegia.
Total, 7 cases.				Average cell count 5/3.

Three cases in this group showed "characteristic" reactions whilst the reactions of the other cases differed. Although the average cell count was 5/3, it should be mentioned that it was 11/3 in the case of chorea, 10/3 in a case superimposed on mental deficiency, and only 1/3 in the case of hereditary paraplegia.

9. "Atypical" Psychoses.

Pandy.	Nonne.	Takata.	Cases.	Clinical remarks, etc.
—	—	—	1	} See discussion.
—	—	L. ± to W. +	10	
—	F.Tr.	L.Tr.	1	
—	±	W. +	1	
±	—	L.Tr.	1	
Total, 14 cases. Average cell count 9/3.				

It is remarkable to note that in these cases the Takata reaction was "late" in 12 out of 14 cases, Pandy and Nonne being negative in 11 cases and the average cell count being slightly but definitely increased.

10. Cases with Disputed Diagnoses.

Pandy.	Nonne.	Takata.	Cases.	Clinical remarks, etc.
—	—	F.Tr.	1	Paranoid dementia?. Involuntary psychoses with depressive paranoid delusions and auditory hallucinations.
—	—	W. +	1	Paranoid dementia?. Auditory hallucinations in beginning organic dementia.
—	—	W. +	1	Paranoid schizophrenia?. Recurrent mania with paranoid features. Slight disturbance of thought and scanty psycho-motor symptoms.
—	±	Tr.	1	Paranoid schizophrenia?. Atypical mania?.
—	L.Tr.	+	1	Paranoid schizophrenia?. Alcohol hallucinosis.
Total, 5 cases. Average cell count 4/3.				

In three of these cases the reactions were characteristic. In one of the other two cases (involuntary psychosis) the Takata reaction was weaker than is usually found in schizophrenia and this may be in favour of the diagnosis of involuntary psychosis. In the other case the diagnosis of alcohol hallucinosis may be supported by a relatively strong Nonne and strong positive Takata reaction.

DISCUSSION.

The material presented here and the results obtained on 165 cerebrospinal fluids can be divided into three groups:

1. Organic Neurological Cases and Syphilitic Conditions including G.P.I.

The fluids of these 49 cases were usually characterized by some positivity of all three protein reactions. The results of the first communication are confirmed, "that the modified Takata reaction is superior to the Pandy test usually made in the routine examination of cerebrospinal fluid," and the present series also shows that it is superior to the Nonne test. Again, in a number of organic neurological cases, the modified Takata reaction was the only reaction indicating some disturbance in the protein composition of the cerebrospinal fluid. Sometimes, however, the Pandy and Nonne tests were stronger than the modified Takata reaction—a state which may have been due to an absolute or relative increase in the "albumin" fraction. This was clearly demonstrated in the case of commencing cerebrospinal meningitis, where Nonne and Pandy reactions were much stronger than the very late positive modified Takata reaction. Otherwise the Nonne test was positive 30 times in these cases, while Pandy was positive in 23 cases only.

2. "Organic" Psychoses.

The group of so-called "organic" psychoses and psychoses with organic complications showed characteristics similar to those of the organic neurological group, although on the whole the reactions were less strong. Again, the Nonne test was more frequently positive than the Pandy, as was demonstrated in the group of "complicated" involuntional psychoses. The Nonne gave a positive result in six cases against one positive Pandy reaction. The negative results of all three protein reactions in a case of very typical involuntional depression and the late doubtful result of the modified Takata reaction in a case of mild paranoid depressive delusions seem to be in agreement with the results described below on the group of emotional psychoses. On the other hand, not too much attention should be paid to the results obtained in two cases only. Broadly speaking, there appear to be slight pathological changes in the cerebrospinal fluid of quite a number of so-called involuntional melancholias—a fact which is borne out by the clinical picture, namely, in some of these cases, slight organic neurological symptoms were confirmed by weak positive protein reactions, while in others, a second more careful clinical examination carried out after the results of the fluid examination had been obtained revealed the presence of mild organic neurological disorders.

3. Non-organic Psychoses and Personality Disorders.

The fluid findings in the groups of hysterical, neurotic and manic and depressive states were such as one might expect—negative or only doubtful reactions and a low cell count of 1/3 and 2.5/3 respectively, but the groups are small and moreover complicated by external factors in a few cases. This being so, it is deemed wiser not to discuss these groups at the present moment.

The reaction has also been carried out on 79 cases showing definite "schizophrenic" symptoms (49 typical schizophrenics, 4 schizophrenics showing some peculiarities with regard to the state of the disease or symptoms, 14 "atypical" cases, 5 cases with disputed diagnoses, and 7 cases of schizophrenia superimposed on other conditions). It appears justifiable to discuss them in some detail.

In the 49 typical cases the modified Takata reaction usually appeared in the first 3–5 minutes and the turbidity increased during the first 30 minutes to give a weak positive (varying from trace to weak positive). In 28 of these cases Nonne and Pandy tests were negative, and in 11 other cases the Nonne was doubtful and the Pandy negative. In a further 7 cases both Nonne and Pandy were doubtful and in 3 cases the Pandy reaction was doubtful with a negative Nonne reaction. The average cell count was 5/3. So it appears that with the absence of organic symptoms the reaction type of "weak positive modified Takata reaction together with negative or doubtful Nonne and/or Pandy reactions" is "characteristic" (although, of course, not "specific") for clinically typical cases of schizophrenia. In another 4 cases which had to be considered as schizophrenia the protein reactions were not "characteristic." These cases showed some peculiarities with regard to their development, clinical state, etc., which may, but of course need not, explain this difference in reaction type. In 5 other cases the diagnosis was disputed, and 14 cases were considered to be "atypical," the latter ones showing such a mixture of manic-depressive and schizophrenic symptoms that it was felt that they fitted neither the diagnosis of schizophrenia nor manic-depressive psychosis. It has often been stated that one finds a relatively adequate emotional response in female schizophrenic patients which is likely to upset the diagnosis, but it can be stated that 10 of these 14 cases were male patients. Twelve out of these 14 were characterized by late modified Takata reactions. Only one of these cases showed a "characteristic" reaction with a cell count of 17/3, and this case had been diagnosed as "paranoid schizophrenia" elsewhere. Further examination of cases, "atypical" from either the clinical or laboratory point of view, similar to the 23 just mentioned, are most desirable for diagnostic and prognostic reasons (especially with regard to treatment).

Three of the cases of schizophrenia superimposed on other conditions also gave "characteristic" reaction types. Among the remainder of the 165 cases, only 11 showed reactions similar to the "characteristic" type. One of them, diagnosed as involuntional melancholia, had auditory hallucinations and paranoid delusions. Three cases were of a neurological nature, epilepsy, old hemiplegia and sciatica,

and 6 cases were suffering from syphilis. Cases of this latter type usually give rise to a disturbance of the albumin-"globulin" ratio of the cerebrospinal fluid.

The results obtained with the modified Takata reaction in combination with Nonne and Pandy reactions support the view that the changes found may be due to a change in the albumin-"globulin" ratio in the cerebrospinal fluid. The Nonne reaction, which is considered to be specific for "globulin," was positive in 75 cases, against a positive Pandy reaction occurring only in 43 cases in this series of 165 cases.

The results obtained in schizophrenics generally confirm the findings of Kafka and Samson (3), and Neel and his collaborators (4 and 5), using more complicated methods.

SUMMARY.

A modified Takata reaction, together with the usual routine tests carried out on cerebro-spinal fluid, has been applied to the cerebrospinal fluids of organic and non-organic neurological and psychiatric cases.

The results of the gross organic neurological group confirmed previous observations on the value of the Takata reaction on cerebrospinal fluid.

In "organic" psychoses the modified Takata reaction is often weak positive in a number of cases, together with a slight Nonne and/or Pandy reaction.

The tests have also been used on nearly 80 cases of "non-organic" psychoses. If attention is paid to finer variations of the results, changes in the cell and protein content of the cerebrospinal fluid will be found in a surprisingly great number of "non-organic" psychiatric cases. These changes appeared to be most outspoken in the group of "schizophrenia." It appears to be characterized by a weak (trace to weak positive) Takata reaction, with the other tests negative or doubtful, and an average cell count of 5/3.

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