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Part I.—Original Articles.

The Cerebro-Spinal Fluid in Certain Mental Conditions.

(An Essay for which was awarded a prize by the Medico-Psychological Association, 1911.) By WILLIAM BOYD, M.D., Assistant Medical Officer, Inverness District Asylum.

THERE is a constant endeavour in psychiatry, as in other branches of medical science, to distinguish between organic and functional disorder. Year by year, in most of these other branches, the organic group becomes larger, the functional group smaller. But unfortunately the same cannot be said for psychiatry. When all is said and done, the term "functional disease" is largely a cloak for ignorance. Where there is disease there must be something to show for it, but if the changes are so subtle as to escape detection, we at once label the condition "functional." General paralysis was considered a functional disease until it was proved to have a very solid anatomo-pathological basis; indeed, until this proof was forthcoming it could hardly be said to exist as a definite entity at all. Until this process is extended to other forms of insanity, clear thinking in psychiatry is impossible. We are still far too prone to look only upon the mental side of the cases which come under our care, whereas we ought diligently to search for some physical causal factor that may be at work, and for corresponding physical changes that may give us a clue to such a factor.

Dr. L. C. Bruce and the numerous workers who have followed in his steps have shown how fruitful a line of investigation this may prove in the case of the blood. It is quite as probable, however, on *à priori* grounds, that a study of the cerebro-spinal fluid, which comes into such intimate contact with every part of the central nervous system and plays the part of the lymph of the brain, as Mott (1) has pointed out, will yield results of equal value. And yet, up to the present, such results have been conspicuous by their absence except in the case of general paralysis. It is inconceivable, however, that the lymph of the brain should be normal when the brain itself is so profoundly affected as in the acute insanities, and the present research is an attempt to decide whether or not the negative results of some previous observers must really be regarded as final. Most of the work has been done in the Derby Borough Asylum, but a number of nervous and other diseases were investigated in Dr. Byrom Bramwell's wards in the Edinburgh Royal Infirmary. Altogether 170 punctures were made in 120 patients. The observations extended over a period of twenty-nine months.

A large amount of work has been done upon the cerebro-spinal fluid, but attention has been directed hitherto mainly to general paralysis and the allied parasyphilitic condition tabes dorsalis, and few references to the ordinary insanities are to be found; it is to these latter cases that I have devoted special attention.

On looking through the literature I have been struck by the fact that one rarely finds a description of the fluid on more than one occasion, or anything in the nature of a comparison between the different conditions of the fluid which may obtain in the same case on different occasions, and yet, in investigating the conditions of, say, the blood in various affections, no one would think of resting satisfied with a single examination. It is true that there is this important difference between the two cases, that a blood examination is a mere trifle, which may be repeated as often as desired, whereas a lumbar puncture is a definite surgical proceeding, entailing considerable discomfort to the patient, and in some cases (as will be seen later) very disagreeable after-effects. For these reasons it is sometimes impossible to get the patient's permission for a second puncture. Nevertheless it is very

desirable that series of observations should be made for two reasons: (1) A good indication is afforded as to the reliability of the technique; if fairly constant results be obtained, the technique is satisfactory for comparative purposes; (2) changes in the fluid are shown which may give very valuable indication of corresponding changes in the brain and its meninges.

Physical and Chemical Properties.

The normal cerebro-spinal fluid is clear and colourless, with a specific gravity of 1006 to 1008. It contains no albumen, but a trace of serum-globulin and albumose, and a substance which reduces Fehling's solution. This substance was considered until recently to be pyrocatechin, but authorities are now returning to the original view of Claude Bernard that it is glucose. The normal fluid is very poor in cellular elements, an occasional lymphocyte being met with, but never a polymorphonuclear cell. In disease the cells may undergo considerable change. Thus, in acute suppurative meningitis the fluid is found to be swarming with polymorphonuclear cells, and instead of being clear and limpid becomes thick, yellow and turbid. In the subacute and chronic affections of the meninges a lymphocytosis is the rule. It is probable that further work will show the exact type of mononuclear cell which is present to be of importance, but at present all such cells are classed together as lymphocytes, the small variety as a rule preponderating. The fluid is alkaline in reaction, the alkalinity being only half that of the blood. It contains chlorides, carbonate, phosphates, and urea in minute quantities. Any of the above may vary in disease, but in the present investigation attention has been mainly directed to the cytology, the protein content, and the Fehling-reducing power.

Cytology.

The method employed for enumerating the cells was that of Widal, which consists in centrifuging 5 c.cm. of the fluid until all the cells have been drawn to the bottom of the tube, the time required depending on the speed of the centrifuge, decanting the supernatant fluid, and inverting the tube for half a minute so as to drain it well; the bottom of the tube is

then scraped with a capillary pipette, and the drop thus obtained blown on to a cover-glass, care being taken not to spread it out, otherwise the concentration is seriously affected. It is allowed to dry, and the film may be fixed in a mixture of equal parts of absolute alcohol and ether, after which it is stained with methylene blue, Jenner's stain, or Pappenheim's pyronin-methyl-green, the last-named having a selective action on the plasma-cells met with in general paralysis. In nearly every case ten consecutive fields have been counted under a magnification of 450 diameters and the average taken.

It has been objected to this method that it is inaccurate, and it must of course be admitted that it does not give the total number of cells present in a given quantity of fluid, but, after all, what we want to know is the relative numbers in different cases, and on different occasions in the same case. With the object of attaining greater accuracy Fuchs and Rosenthal in 1904 used the ordinary hæmocytological technique, and by means of a pipette, counting chamber and staining fluid estimated the number of cells per cubic centimetre. It has been shown, however, that when only a few cells are present the error varies from 30 to 90 *per cent.*, and the field method of Jones yields no better results.

Proof of Accuracy of Method Used.

As has already been pointed out, the accuracy of a method can be gauged to a certain extent by comparing the results obtained on different occasions from the same case. Of course, it is always possible that variations may be due to changes in the fluid itself and not to inaccuracy in the technique, but if the case presents exactly the same clinical symptoms throughout, and if only a short interval of time separates the different examinations, then it may fairly be claimed that the results will afford a satisfactory indication as to the reliability of the technique.

It is with this object that Table I has been prepared. A study of this table will show that in only one case (No. 6) does a serious discrepancy occur which cannot be explained. It is true that when the cells number several hundreds there are some marked differences in the counts, but from the practical point of view this is of little import, because what we really

want to know is (1) if a lymphocytosis is present, and (2) if it is marked in extent. In No. 18 the eighty-four cells were present when the fluid was withdrawn shortly after the patient had had a severe epileptic fit. What may be the relation between the two conditions—fit and cytosis—it is impossible in the present state of our knowledge to say, but that there is some relationship, such as a common causal factor, I am convinced. The difference between the first two counts in No. 19 is capable of a similar explanation, and the case will be considered more fully later. In No. 6 there was an interval of six months between the two punctures, but the condition of the patient had not changed in the interval, and it is probable that the low count on the first occasion was due to faulty technique. With this single exception, however, the results have been so uniform as to justify one in saying that the Widal method is perfectly satisfactory for purposes of comparison. When the initial count has shown no cellular increase, the subsequent counts, with this one exception, have also proved normal. When, on the other hand, a lymphocytosis has been present on the first occasion, it has always been met with on subsequent occasions, in some cases varying considerably, as was only to be expected, but in others maintaining a remarkably constant level. It would be interesting to learn if a similar series of observations with the method of Fuchs and Rosenthal yielded any more constant results.

What constitutes a Lymphocytosis?

Having decided upon the technique to be used, the next point to be considered is: What constitutes a lymphocytosis, *i.e.* within what limits may the cell-count be considered normal? Here, again, there is considerable difference of opinion. In the cases where the cells can be counted by the hundred there is no difficulty, but it is in the doubtful cases that some definite standard must be fixed upon. According to Purves Stewart (2), after 5 c.cm. have been thoroughly centrifuged not more than four cells should be seen in the field with a magnification of 450 diameters. I consider that with a similar magnification nine or ten cells may be present without justifying one in calling the fluid abnormal, but that anything above that number must be regarded as pathological.

Turning now to the results obtained, as shown in Table II, we must divide the cases into two classes :

(1) A group containing the parasyphilitic diseases—tabes dorsalis and general paralysis.

(2) A group comprising the remaining cases.

(1) *Cytology of the Parasyphilitic Conditions.*

There can be no question that the earliest and most reliable indication of the onset of general paralysis and tabes dorsalis is afforded by the cerebro-spinal fluid. Since Widal, Sicard, and Ravaut (3) in 1900 first described the presence of a lymphocytosis in these diseases, a mass of evidence has been accumulating, which goes to prove that in almost every case there is an increase of the mononuclear cells, an increase which may be large or small, but which is distinct, and which, moreover, is most marked in the early stages of the disease.

My own results fully bear out the constant character of the lymphocytosis in tabes and general paralysis. From a study of Table II it will be seen that in every case of general paralysis the cell increase was marked, in no instance falling below 40, and in one remarkable case reaching the unprecedented number of 3400. This case was a typical one of general paralysis in an early stage, presenting no unusual features. The fluid was examined as many as seven times and by independent observers, and on each occasion this enormous lymphocytosis was present. I draw attention to this case because, so far as I have been able to ascertain, this leucocytosis easily holds the record.

In only two cases of tabes was the count below 20. In one of these the only symptoms were loss of the knee-jerks, the Argyll-Robertson pupil, and syphilitic ulceration of the larynx. The other presented a perfect clinical picture of the disease, and yet on the two occasions that the fluid was examined the count never rose above 14. The case of taboparesis and the other nine cases of tabes all showed a marked lymphocytosis.

Thus in every case of tabes and general paralysis a distinct lymphocytosis was present, and in the great majority of the cases it was well marked. These results are in perfect accord with those of previous observers.

(2) *Cytology of the Ordinary Insanities.*

Turning now to the second group, which to me is by far the more interesting. and yet has had much less attention paid to it, one is confronted with a much more difficult problem, and it is here that the results of other observers are of great interest. Pegna (4) and Purves Stewart (5) both assert in the most categorical way that the cytological examination of the cerebro-spinal fluid in mental disease always yields negative results, and Winifred Muirhead (6) did not obtain a single positive result in seventy-seven cases of the ordinary psychoses. Williamson (7), on the other hand, got a high cell-count in six cases of insanity divided between epileptic and acute mania, and he considers that a cellular increase may occur in any of the conditions of excitement.

It is of importance to note that in ordinary physical disease, as distinguished from insanity, a cytosis may occur in a number of toxic conditions, such as tubercular meningitis and herpes zoster. Some interesting observations have been made quite recently upon that most typically toxic of all nervous diseases, namely, acute anterior poliomyelitis, and Flexner and Clark, of New York, describe a well-marked cellular increase in this condition, both experimentally in monkeys and clinically in man.

The consensus of opinion appears to be, therefore, that a high cell-count is met with in the nervous lues and a few other physical conditions, but that it never occurs in mental disease.

To these conclusions my own results are strongly opposed. From Table II it will be seen that out of a series of 119 cases in 71 was the cell-count below ten, whilst in 48 it was above ten, and therefore to be considered pathological. If from these 48 cases are subtracted 10 cases of tabes, 1 of tabo-paresis, 12 of general paralysis, and 1 of acute suppurative meningitis, there is left a group of 24 cases in which the cell-count was above the normal, and in which there was no history or evidence of syphilis, except in the case of aneurysm, which was definitely syphilitic, and two of the cases of cerebral tumour. It must not be imagined that these figures—24 out of 119—represent the true proportion of such cases to the whole, for just as the general paralytics were picked out,

so were those cases chosen which seemed likely to fall into one of the classes about to be described. Nevertheless, the fact remains that in a small asylum quite a number of such cases could be found.

Of these 24 cases those of aneurysm, chronic mania and alcoholic excitement may be dismissed with a word. The cell-count was 14 in the two former, and 12 in the latter, an excess over the normal which is too small to justify one in drawing any conclusions; moreover, in the first case the syphilitic element was present, while the other two were just those conditions in which, judging from Williamson's observations, one would expect a slight cellular increase.

There are now left 21 cases which showed a lymphocytosis, and this number is made up as follows: Congenital imbecility 2 cases, cerebral tumour 3 cases, epileptic insanity 5 cases, a group which I have provisionally called dementia præcox 10 cases, and a case of melancholia, which very possibly should be included in the preceding group.

In one case of congenital imbecility the cell-count was 25, in the other it was 18 on one occasion, 19 on the next. It may be mentioned that Otto Rehm also obtained a positive cytological result in two cases of imbecility.

Of the three cases of cerebral tumour, one was diagnosed as a gumma in the region of the optic chiasma, and it produced a lymphocytosis of 21. Under anti-syphilitic treatment all the symptoms disappeared and the lymphocytosis fell to 10.

The second was also a case of gumma of the brain, with a lymphocytosis on admission of 110. The patient was obviously suffering from some acute cerebral condition, as there was severe headache, loss of power in the left arm, rapid loss of sight, and a condition of increasing coma, but owing to the marked lymphocytosis and a history of an old syphilitic left hemiplegia which was successfully treated two years previously, energetic anti-syphilitic treatment was adopted. The coma became deeper, however, and in five days the patient died. Shortly before death the cerebro-spinal fluid was again examined and was found to be turbid, the turbidity being due to enormous numbers of polymorphous leucocytes. A differential count was made and showed that there were 57 polymorphs to 43 lymphocytes. At the autopsy the remains of an old gummatous lesion were found at the posterior

end of the first right frontal convolution—this was the cause of the lymphocytosis. Two acute abscesses were present, one in the right motor area, the other in the left occipital lobe, and the pus from the latter abscess had made its way into the lateral ventricles, and thence to the base of the brain through the locus perforatus posticus—hence the polymorphonuclear leucocytosis. The importance of this case lies in the fact that the change in the cerebral condition was faithfully represented by the change in the cerebro-spinal fluid. In both of these cases, therefore, the lymphocytosis was due to a syphilitic lesion.

In the third case, however, there was no history or evidence of syphilis. Anti-syphilitic treatment had been tried for years without avail. At the autopsy the tumour, which involved the pituitary body, was found to present none of the characteristics of a syphilitic lesion, and on microscopical examination it showed the appearance of a mixed-celled sarcoma. Yet the cell-count reached the enormous number of 1630. Here we have a demonstration that a very marked cerebro-spinal lymphocytosis may be present quite apart from any syphilitic process.

Of the five cases of epileptic insanity in which a lymphocytosis was observed, two had between 20 and 40 cells, one having 30 on one occasion and 20 on another, while the other had 29 on the first occasion and 28 on the next. As a number of months elapsed in each case between the two examinations, it is obvious that the high cell-count could not be put down to a mere accident. In neither of the cases was a trace of excitement present, nor were they subject to periodic attacks of excitement. In the other three cases the increase in cells was more marked. One had a count of 54, which fell to 28 on a subsequent occasion. In the second there were 84 cells, but in this particular case the fluid was withdrawn shortly after the patient had taken a fit. On three subsequent occasions the counts were 14, 23 and 38. I am not prepared to say what relation the cytosis bore to the fit.

The third case was altogether exceptional, and is really in a class by itself. The patient was a man, æt. 53, who was admitted in September, 1910, in a restless excited condition, with marked delusions and hallucinations of a religious nature. Three years previously he had sustained an injury to

the head, and since then had had three or four fits of an epileptiform nature, but had not had any for some months prior to admission. An examination of his cerebro-spinal fluid on admission showed that he had only 6 lymphocytes per field, and these were all of the small variety. He soon settled down and became quite quiet and rational until March 10th, 1911, when he had a severe epileptic fit, became very restless, noisy and excited, and developed the most vivid visual and auditory hallucinations. His cerebro-spinal fluid was examined on March 13th, and it was found that he had a lymphocytosis of 39; of these, 68 per cent. were small lymphocytes and 32 per cent. were large lymphocytes. The fluid was examined on March 14th, 15th, 16th, and 17th, and a lymphocytosis was present on each occasion, the last count being one of 80. The differential count was very constant throughout. This is the only case I have encountered, with the exception of the case of cerebral gumma and abscess already described, in which a marked change in the cerebro-spinal fluid occurred in the course of the disease. Here, again, the task of explaining the relationship between fit and cytosis is an almost impossible one in the present state of our knowledge; but I consider that the cytosis was not due directly to the fit, but that both fit and cytosis had a common toxic origin.

Out of a series, therefore, of 15 cases of epileptic insanity, in five cases was there a well-marked increase in the cell-count, this increase being present, although varying in extent, on the different occasions on which the fluids were examined.

There are now left ten cases of dementia præcox and one of melancholia. These are the most important and at the same time the most difficult cases of the series. It will be noted that in most of the cases of dementia præcox the lymphocytosis was moderate although quite decided; but in one case it amounted to 121, being 85 some months later. I have called the cases dementia præcox, but I do not wish to imply that they all presented perfect clinical pictures of that disease; rather have I classed them thus, because they were all young adults. The symptoms had a vagueness which one is only too apt to associate with dementia præcox, and one of the chief features was that lack of emotional response which is stated to be one of the most important points in the diagnosis of this condition.

I am not concerned, however, with questions of nomenclature. What I wish to emphasise is that here is a group of cases bearing a family resemblance to one another, in every one of which there was a marked change in the fluid which bathes the brain and receives the products of neuronic metabolism. Some of these cases were hopelessly demented, others were progressing towards dementia; but a few seemed to have remarkably little the matter with them. These last were dull, listless and apathetic, with little interest in life, but they were certainly not cases in which one would expect to find evidence of any profound change in the nervous system. The first case or two which I encountered caused me great surprise, but when I came to recognise the symptoms—they are hardly worthy of the title of syndrome—I found that I was able to forecast with some degree of certainty the cases in which this change would be found; they nearly all belonged to the "lymphatic type." According to Stoddart (9) dementia præcox may be regarded from one point of view as a failure in evolution, and he points out certain similarities between that condition and idiocy and imbecility. (In two of my cases of imbecility there was a moderate lymphocytosis.) One got the impression that in every one of these 10 cases there was a congenital element present, more marked in some cases than in others. In 5 cases the fluid was examined on more than one occasion, and each time an increased cell-count was present. A blood examination was made in every case, but no abnormality was detected.

These cases are, to my mind, of such importance that I deem it advisable to give a brief summary of the salient points in each case.

CASE 1.—A. S—, female, æt. 21. Paternal aunt is insane. Admitted to the Derby Borough Asylum in October, 1909. For a year previously she had been losing energy and interest in life, and would sit for hours gazing vacantly in front of her. On admission she was dull, stupid, and apathetic, with slow mentation. She was in poor physical condition, but without any actual disease. Habits wet and dirty. She became somewhat brighter, habits improved, and she began to employ herself, but is now *in statu quo*. She is in a dull, phlegmatic condition, with complete loss of memory. There is not a trace of emotional response; thus, when told of the death of her mother,

to whom she was much attached, she showed no sorrow or grief; joy is similarly unknown to her. The cell-count on three different occasions was 31, 54, and 26. The protein content was increased.

CASE 2.—A. S—, male, æt. 25. A half-sister is insane. Admitted in July, 1910. He is said to have been rather "soft" and below the average intelligence all his life. On admission he was stupid and confused, understood little of what was said to him, but assented in a facile way to any suggestions that were made. Habits wet and dirty. He remained in this condition for about a year, and then improved to a certain extent. At present he is weak-minded and facile, and seems to be incapable of experiencing joy or sorrow. The cell-count on two occasions was 121 and 85. The protein content was not increased.

CASE 3.—H. W—, male, æt. 21. On admission, April, 1910, he was very stupid and confused, but the salient feature of the case was his silliness—his laugh was an inane cackle, he made absurd grimaces, and indulged in the most ridiculous antics. He developed katatonic symptoms, such as *flexibilitas cerea*, and struck attitudes all day long. He showed, in addition, symptoms of negativism. After nine months he began to improve, but is still childish and simple, with impaired memory. The cell-count was 20, and the protein content was not increased.

CASE 4.—E. B—, male, æt. 30. A brother is insane. Patient was a sharp and clever youth up to the age of seventeen, when he began to degenerate both physically and mentally. He was admitted in January, 1910, and it was found that he had not had his clothes off for a year. He was dull and apathetic, and seemed to have little hold upon life. He has improved considerably, and is now able to converse rationally and to employ himself usefully, but he is still simple, facile, and childish. The cell-count was 41, and six months later it was 27. The protein content was not increased.

CASE 5.—A. M—, male, æt. 21. Has always been of a weak type. Admitted in February, 1909, in a confused condition, staring vacantly about him, rambling and incoherent in his talk, with delusions of persecution. He remained in this condition for a year, and then began to get more rational. He can now talk coherently, and works in a mechanical way, but

is facile and simple-minded. The cell-count was 20, and the protein content was not increased.

CASE 6.—A. K. W—, female, æt. 33. Father was insane Patient has always been of a highly strung, neurotic temperament. She broke down under the strain of nursing, became rambling, foolish, and unduly sentimental, and finally grew extremely violent. Since admission (January, 1911) she has rapidly gone downhill, her habits are faulty and degraded, and she seems to be passing into a condition of dementia. She has motor symptoms of the katatonic type, such as *flexibilitas cerea*, echolalia, stereotypy, and negativism to a marked degree. The cell-count was 70, and the protein content was not increased.

CASE 7.—F. H—, female, æt. 25. Paternal aunt and grand-aunt were insane. Admitted in April, 1909, and was then depressed, suspicious, and delusional. At times she is noisy, excited, and abusive. She has been steadily drifting into dementia, and the loss of emotional reaction is very marked in her case. The cell-count was 19, and the protein content normal.

CASE 8.—T. P—, male, æt. 34. Admitted in 1904. He was transferred from another asylum, where he had been for a year. He was said to have been always somewhat weak-minded, and on admission here was diagnosed as a case of primary dementia. He is now in a condition of profound dementia, and leads a vegetable existence. The cell-count was 15, and on a subsequent occasion it was 14. The protein content was normal.

CASE 9.—P. J—, male, æt. 35, but was only 19 years old when admitted. Prior to admission he was dull, depressed, and seclusive, shutting himself up, and refusing to associate with other boys. On admission he is said to have been dull and lethargic, furtive and suspicious. He showed no signs of improvement, and gradually drifted into a condition of profound dementia. The cell-count was 26, on two subsequent occasions being 21 and 22. The protein content was normal.

CASE 10.—F. H—, male, æt. 42, but was only 23 years old on admission. There was hereditary predisposition to insanity. He was formerly a medical student in Edinburgh University, but broke down and was admitted in a state of acute excitement. He soon became quiet, but remained in a foolish, childish condition, laughing and talking to himself,

striking attitudes, making absurd gestures, and gradually becoming more and more demented. He is now profoundly demented and extraordinarily incoherent. The cell-count was 23 on one occasion, 33 on another. The protein content was not increased.

There remains to be considered the very interesting case which I have placed under the heading "melancholia," but here, again, the name is apt to be misleading. Indeed, I am inclined to think that it would be more correct for some reasons to place her in the class just described; she is certainly not a typical case of melancholia.

The patient is a woman, æt. 28 years, who for some months prior to admission had been listless and somewhat depressed, but her chief characteristic seemed to be that she had lost her hold upon life, and did not care very much one way or the other what happened to her. She remained dull and apathetic for some time, and then gradually began to take an interest in what went on around her, and to occupy herself usefully, but even now (nine months later) her emotional reaction is very low. At no stage, however, could one have said definitely that she was insane, for the depression hardly attained to pathological limits. And yet there were very marked and constant changes in the cerebro-spinal fluid. It was examined on four occasions at intervals of two or three months, and on each occasion a very great cellular increase was present, the figures being 103, 340, 120, 270. The mental improvement has, therefore, not been accompanied by a corresponding change in the cerebro-spinal fluid. The protein content was distinctly increased each time. In this case there was no history of syphilis or of miscarriage, and the most thorough examination failed to reveal the slightest evidence of syphilitic infection. The nervous system appeared to be perfectly normal.

Summary of Cytological Results.

(1) For practical purposes of comparison between different cases the field method of Widal is, on the whole, "satisfactory."

(2) Repeated observations on the same case sometimes yield results of great value.

(3) The results obtained in the parasyphilitic conditions were in accord with those of other observers. In every case of

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general paralysis there was a marked cellular increase, and in only two cases of tabes was it not well marked.

(4) In one case of non-specific cerebral tumour there was an enormous lymphocytosis. A very high cell-count, therefore, does not necessarily imply the presence of nervous lues, as has been considered hitherto.

(5) Conditions of excitement seem to have no influence on the cell-count; in thirteen cases of acute mania the count was normal every time, and in only one case of chronic mania was it raised, and that only to a very slight extent.

(6) Certain cases of epileptic insanity showed a lymphocytosis, but in what way they differed from cases in which the fluid was normal has not been determined.

(7) Two cases of congenital imbecility without evidence of syphilis gave a positive result.

(8) Ten cases bearing certain features in common, together with an eleventh case closely resembling them, gave a well-marked cellular reaction. These cases bore no relationship to syphilis, to epilepsy, or to any form of excitement.

Protein Content.

Many methods have been used for estimating the protein content of the cerebro-spinal fluid, but the majority of these have proved unsatisfactory. In the present investigation two recent methods have been employed, and results of considerable interest have been obtained. These methods are the butyric acid test of Noguchi, and the ammonium sulphate ring test of Ross and Jones. Both of these tests depend upon precipitation of the globulin present, which constitutes the main bulk of the protein. Before applying either test it is essential to make certain that there is no blood in the fluid.

Noguchi's test consists in the addition of 5 c.cm. of 10 per cent. butyric acid to 2 c.cm. of cerebro-spinal fluid with the application of heat, 1 c.cm. of a 4 per cent. solution of sodium hydrate being then added with a further application of heat. A positive result is indicated by the appearance in a few minutes of distinct flocculi, which are very fine at first, but gradually become coarser, and eventually fall to the bottom of the tube in the form of a precipitate. It has been claimed that this test is specific for general paralysis and tabes.

In the Ross-Jones reaction 1 c.cm. of cerebro-spinal fluid is run on to the surface of 2 c.cm. of a saturated solution of neutral ammonium sulphate. A positive reaction is indicated by the appearance of a ring at the junction of the two fluids, a ring which ought to be clear cut and of the thickness of a sheet of paper. An indistinct haze is taken as being negative. In order that the faintest ring may be detected it is essential that powerful indirect illumination, together with a black background, be used. The time in which the ring appears varies in different cases. I have taken five minutes as the limit. If the ring does not appear in that time the test is regarded as negative.

In order to make the test a quantitative as well as a qualitative one the fluid was diluted, and that degree of dilution noted with which the ring could just be obtained. This appears to be as simple and satisfactory a method of quantitative examination as any that has hitherto been used. In carrying out this method it is of the utmost importance that the conditions under which the test is performed should be constant, for if varying illumination and background be used the results will be found to vary correspondingly. I tested the accuracy of this dilution method by applying it to the fluid of the same case on a number of different occasions, and the results are embodied in Table III. From this table it will be seen that in the majority of cases there was remarkably little variation in the results, and this marked uniformity leads one to venture the opinion that in the dilution method we have a simple and accurate means of estimating the protein content.

Turning now to the results obtained by these two methods, we find that in general paralysis and tabes, the results, as shown in Tables IV and V, are identical with those obtained by previous observers, there being in every case a very distinct increase in the protein content. In one case of general paralysis and in one case of tabes so great was the amount of globulin present that a distinct reaction was obtained with the ammonium sulphate test when the fluid was diluted twelve times. On the other hand, one typical case of general paralysis with a large lymphocytosis only gave a positive reaction with a dilution of 1 in 2, and as in seven other cases of insanity a positive reaction was obtained with a similar dilution, repeated examination of this case was carried out. On five occasions a

similar result was obtained, but on a sixth occasion a ring was obtained with a dilution of 1 in 4.

In the case of the non-syphilitic diseases, however, my results are opposed to those of certain previous observers.

From Table IV it will be seen that a positive or doubtful Noguchi reaction was obtained in one case of pituitary tumour (non-syphilitic), in 2 out of 10 cases of dementia præcox, in 4 out of 15 cases of epileptic insanity, and in 1 out of 9 cases of melancholia. This last case is the one which has already been mentioned as closely resembling the dementia præcox group; the reaction was positive each time the fluid was examined. In none of these cases, however, was it anything like so marked as in the cases of general paralysis and tabes dorsalis. In 81 other cases the test was negative. In only one case (epileptic insanity) was a positive result unaccompanied by a lymphocytosis.

The ammonium sulphate test was positive in 46 out of 87 cases—at least a ring was obtained (see Table V). Subtracting the 10 cases of tabes and general paralysis we are left with 36 positive results. Of these, 26 gave the ring only with undiluted fluid. I consider that if the above-mentioned precautions be adopted and a period of five minutes allowed to elapse, the appearance of a ring at the end of that time is not to be regarded as a pathological sign, provided that the ring be lost when the fluid is at all diluted. In many normal conditions a faint but distinct ring may be seen if the very best illumination be used. Very different is the ring in general paralysis, which comes at once and is very marked. This leaves only 10 cases which gave a distinctly pathological result. These cases being analysed stand as follows: One case of pituitary tumour with an enormous increase in the globulin, one case of acute mania, one case of melancholia already described as closely resembling the dementia præcox group, one case of dementia præcox, four cases of epilepsy, one case each of alcoholic excitement and congenital imbecility.

It is therefore incorrect to say that in no form of insanity except general paralysis does a sufficient increase of the protein content occur to give positive results with the butyric acid and ammonium sulphate tests.

As regards the relation between the two tests it may be noted that:

(1) In no case was the Noguchi test positive without the ammonium sulphate test giving a ring with a dilution of 1 in 2 or upwards.

(2) In a number of cases the ammonium sulphate test was positive with a dilution of 1 in 2 without a corresponding Noguchi, but in dilutions above this the Noguchi reaction was always present.

Fehling Reduction.

Fehling's test was applied in the great majority of cases, and in no case was it found to be negative. The amount of glucose varied somewhat in different conditions, but not in a constant enough way to enable one to draw any definite conclusions. An accurate quantitative estimation was not made. The reaction was feeble in two cases of acute mania, two cases of dementia præcox, and three cases of general paralysis. It was exceptionally well marked in four cases of epileptic insanity, one case of alcoholic excitement, and one case of secondary dementia. In all other cases it seemed to be present in normal amount, with the exception of two cases of diabetes in which a very large quantity of glucose was noted.

After-effects.

On this important and practical point there is remarkable diversity of opinion. Thus Chauffard and Boidin had only 3 cases of vomiting in a series of 223 punctures, and no other ill-effect to speak of, with the exception of a slight headache. Nissl, on the other hand, met with pronounced symptoms in 48 out of a series of 112 cases. These symptoms were headache, nausea and vomiting, and in some cases the patient was completely prostrated ; they came on from five to twelve hours after puncture. He records that seven doctors were lumbar-punctured, and severe symptoms ensued in six of them. Not more than 5 c.cm. of fluid were withdrawn.

My own results correspond with those of Nissl. I am strongly opposed to those who say that lumbar puncture is a trivial procedure which is hardly ever followed by unpleasant after-effects. Of the 120 patients who were punctured 25 suffered severely, and many others to a slighter extent. The

chief symptoms were headache, giddiness, nausea and vomiting, and in a few cases complete collapse. The patients were usually kept in bed for twenty-four hours after the puncture, sometimes for forty-eight hours, sometimes for even longer. The usual amount of fluid withdrawn was 7 or 8 c.cm. The symptoms appeared as a rule soon after getting up, and sometimes the moment the erect posture was assumed, In some cases, on the other hand, no symptoms appeared for twenty-four or forty-eight hours, and then severe headache perhaps accompanied by vomiting might make its appearance. These cases are very puzzling, and I can offer no explanation of them. In one remarkable instance the patient, being a weakly girl, was kept in bed for five days. At the end of that period she got up, and felt all right for seven hours, but then headache and faintness came on which were so severe that she had to return to bed. One patient vomited before getting up.

It is difficult to account for the different results of some observers, and I can only offer one suggestion. The one class of case who suffers no after-effect is the general paralytic, probably because of the great excess of fluid which he possesses. If the series of cases examined consist mainly of general paralytics, there will be few or no after-effects to record, whereas if the proportion of general paralytics be small the number of cases showing after-effects will be correspondingly large.

In many of these cases the symptoms seemed to be medullary in type, and a series of observations were made to determine whether the blood-pressure was affected by the withdrawal of cerebro-spinal fluid, but with negative results.

Conclusions.

(1) It has been recognised for a number of years that investigations on the cerebro-spinal fluid are of great importance in the acute microbic, and also in the syphilitic and parasyphilitic, affections of the nervous system, but the present research shows that results of considerable value are to be attained in other examples of nervous and mental disease.

(2) With regard to general paralysis and tabes dorsalis the views of other observers have been fully corroborated. An increase in the number of the lymphocytes and in the protein content is the almost invariable rule.

(3) This increase is by no means confined to these conditions, as has been commonly supposed. It has been shown that such an increase may occur in a variety of purely mental affections.

(4) A definite group of cases, bearing a strong family likeness to one another, and approximating more closely to dementia præcox than to any other recognised form of insanity, has been isolated; these cases presented a lymphocytosis which was always distinct and occasionally very marked. Query: Is it possible that these cases are in a class by themselves, and ought not to come under any of the heads in our existing classifications?

(5) The butyric acid reaction of Noguchi is characteristic of general paralysis and tabes dorsalis, but occasionally occurs in other conditions.

(6) The ammonium sulphate ring test is also characteristic of these two diseases, but is more commonly met with in other conditions than is the Noguchi reaction.

(7) The method, which has not hitherto been used, in determining the dilution of cerebro-spinal fluid with which the ammonium sulphate test is still positive, is a simple and accurate way of making a quantitative estimation of the protein content.

(8) It cannot be said that the Fehling-reducing substance shows changes characteristic of any one condition. On the whole it tends to be decreased in general paralysis and tabes.

(9) It is the rule, not the exception, for the operation of lumbar puncture to be followed by unpleasant results, especially if the patient be not kept in bed for twenty-four hours. These unpleasant results are not accompanied by any appreciable alterations in the blood-pressure.

The words of Ernesto Lugaro (12) may be quoted in conclusion: "This method of examination has already given valuable assistance in the diagnosis of doubtful cases, and at the same time it has furnished data of the highest interest. Researches of this kind cannot be too much cultivated, because they will certainly add much to our knowledge of the organic processes which form the substratum of mental diseases."

TABLE I.—*Showing the Extent to which the Cell-count varied in the same Case.*

No.	Condition.	Cell-count on different occasions.					
		1	2	3	4	5	6
1	Acute mania	5	3	—	—	—	—
2	" "	4	1	—	—	—	—
3	" "	4	5	—	—	—	—
4	" "	3	5	—	—	—	—
5	" "	7	8	—	—	—	—
6	Chronic mania.	1	14	—	—	—	—
7	Paranoia	1	2	—	—	—	—
8	Congenital imbecility	19	18	—	—	—	—
9	Melancholia	103	340	120	270	—	—
10	Dementia præcox	121	85	—	—	—	—
11	" "	33	23	—	—	—	—
12	" "	31	54	26	—	—	—
13	" "	15	14	—	—	—	—
14	" "	26	22	21	—	—	—
15	Epileptic insanity	54	28	—	—	—	—
16	" "	30	20	—	—	—	—
17	" "	29	28	—	—	—	—
18	" "	84	14	23	38	—	—
19	" "	6	39	26	11	34	80
20	General paralysis	192	291	—	—	—	—
21	Tabes dorsalis	144	150	252	—	—	—

TABLE II.—*Showing the Cell-count in* 119 *Cases.*

Condition.	No. of cases.	Cell-counts.					
		Normal.	Pathological.				
		1–10.	10–20.	20–40.	40–100.	100–300.	300 and over.
Tabes dorsalis	10	—	2	—	2	6	—
Tabo-paresis	1	—	—	—	—	1	—
General paralysis	12	—	—	—	2	5	5
Disseminated sclerosis	3	3	—	—	—	—	—
Cerebral tumour	3	—	—	1	—	1	1
Acute mania	13	13	—	—	—	—	—
Chronic mania	10	9	1	—	—	—	—
Melancholia	9	8	—	—	—	—	1
Epileptic insanity	15	10	—	2	3	—	—
Dementia præcox	10	—	2	4	3	1	—
Confusional insanity	3	3	—	—	—	—	—
Stuporose insanity	2	2	—	—	—	—	—
Paranoia	1	1	—	—	—	—	—
Folie circulaire (excited stage)	1	1	—	—	—	—	—
Alcoholic excitement	2	1	1	—	—	—	—
Congenital imbecility	13	11	1	1	—	—	—
Secondary dementia	4	4	—	—	—	—	—
Acute suppurative meningitis	1	—	—	—	—	—	1
Congenital syphilis	1	1	—	—	—	—	—
Aortic aneurysm	2	1	1	—	—	—	—
Aortic incompetence	1	1	—	—	—	—	—
Diabetes	1	1	—	—	—	—	—
Pharyngitis	1	1	—	—	—	—	—
Total	119	71	8	8	10	14	8

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TABLE III.—*Showing the Extent to which the Protein Content, expressed in Terms of the Dilution of Cerebro-spinal Fluid which gave a Positive Reaction with the Ammonium Sulphate Test, varied in each Case.*

No.	Condition.	No. of times examined.	Protein content on different occasions.					
			Negative result.	Undiluted uid.	Dilution.			
					1 in 2.	1 in 4.	1 in 5.	1 in 6.
1	Acute mania . .	2	—	2	—	—	—	—
2	,, ,, . .	2	1	1	—	—	—	—
3	,, ,, . .	2	2	—	—	—	—	—
4	,, ,, . .	3	—	1	—	2	—	—
5	,, ,, . .	2	—	2	—	—	—	—
6	,, ,, . .	2	1	1	—	—	—	—
7	,, ,, . .	2	—	2	—	—	—	—
8	Chronic mania . .	2	—	2	—	—	—	—
9	Congenital imbecility	2	2	—	—	—	—	—
10	,, ,,	2	2	—	—	—	—	—
11	Melancholia . .	2	—	—	2	—	—	—
12	Dementia præcox .	2	—	—	—	1	1	—
13	,, ,, .	2	2	—	—	—	—	—
14	,, ,, .	2	2	—	—	—	—	—
15	,, ,, .	2	—	1	1	—	—	—
16	,, ,, .	2	1	1	—	—	—	—
17	Epileptic insanity .	2	1	1	—	—	—	—
18	,, ,, .	2	—	2	—	—	—	—
19	,, ,, .	2	—	1	1	—	—	—
20	,, ,, .	3	2	1	—	—	—	—
21	,, ,, .	3	—	—	3	—	—	—
22	General paralysis .	2	—	—	—	—	1	1
23	,, ,, .	6	—	—	5	1	—	—
24	Secondary dementia .	2	1	1	—	—	—	—

TABLE IV.—*Showing Results of the Noguchi Test.*

Condition.	No. of cases.	Positive.	Doubtful.	Negative.
Tabes	2	2	0	0
Tabo-paresis . . .	2	2	0	0
General paralysis . .	7	7	0	0
Pituitary tumour . .	1	1	0	0
Dementia præcox . .	10	1	1	8
Epilepsy	15	2	2	11
Melancholia . . .	9	0	1	8
Other conditions . .	54	0	0	54
Total . .	100	15	4	81

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TABLE V.—*Showing the Protein Content expressed in Terms of the Dilution of Cerebro-spinal Fluid, which gave a Positive Reaction with the Ammonium-sulphate Test.*

Condition.	No. of cases.	Negative result.	Undiluted fluid.	Dilution of cerebro-spinal fluid.			
				1 in 2.	1 in 4 to 6.	1 in 7.	1 in 10 to 13.
Tabes dorsalis	2	—	—	—	—	—	2
Tabo-paresis	2	—	—	—	—	2	—
General paralysis	6	—	—	1	2	2	1
Pituitary tumour	1	—	—	—	—	—	1
Acute mania	12	5	6	—	1	—	—
Chronic mania	5	3	2	—	—	—	—
Melancholia	5	2	2	1	—	—	—
Epilepsy	14	6	4	4	—	—	—
Secondary dementia	4	3	1	—	—	—	—
Dementia præcox	10	7	2	—	1	—	—
Confusional insanity	2	2	—	—	—	—	—
Stuporose insanity	2	1	1	—	—	—	—
Paranoia	1	—	1	—	—	—	—
Folie circulaire (excited stage)	1	1	—	—	—	—	—
Alcoholic excitement	2	—	1	1	—	—	—
Congenital imbecility	14	10	3	1	—	—	—
Congenital syphilis	1	1	—	—	—	—	—
Diabetes	1	—	1	—	—	—	—
Pharyngitis	1	—	1	—	—	—	—
Chronic rheumatism	1	—	1	—	—	—	—
Total	87	41	26	8	4	4	4

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