A Thesis

on

The Cerebro-Spinal Fluid

in certain forms of

Nervous and Mental Disease.

by

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in 3, 1911.

April 1911.
INDEX

Introduction ............................................. 1
Historical ................................................. 5
Physical and Chemical Properties ................. 9
Cytology .................................................... 14
  Discussion of methods ............................... 14
  Proof of accuracy of method used ............... 16
  What constitutes a lymphocytosis? ............... 19
  Results of Cytological examination ............... 20
    1. Cytology of the parasyphilitic conditions ... 21
    2. Cytology of the ordinary insanities .......... 23
  A difficult group of cases ......................... 31
  Summary of Cytological results ................... 47
Protein Content .......................................... 49
Results .................................................... 57
Fehling-reduction ...................................... 68
After-effects ............................................ 72
  Blood pressure ........................................ 78
Blood examination ..................................... 79
Some cases in which the cerebro-spinal fluid .... 81
  presented features of peculiar interest ......... 81
Discussion of results .................................. 98
Conclusions ............................................. 105
Tables ...................................................... 109
References .............................................. 119
The Cerebro-Spinal Fluid in certain forms of Nervous and Mental Disease.

Introductory.

During recent years a large amount of work has been done on the cerebro-spinal fluid. Mott in the Oliver-Sharpes lectures of 1910 mentions that during the last ten years there were abstracts of 187 papers on this subject in the Revue Neurologique. Much useful information has been amassed, but that there is room for further work on the subject will readily be gathered from a perusal of the literature. In a few main points all observers are agreed, but on many others the greatest diversity of opinion prevails.

Thus, according to Williamson the Fehling-reducing body is not glucose and bears little resemblance to any carbohydrate, nor does it give crystals
with phenylhydrazine, whereas Mott (3) states that the substance is certainly glucose, and that with phenylhydrazine it gives the characteristic crystals of osazone which melt at from 105° to 106°. Williamson found that the Fehling reaction was absent in 15 out of 23 cases of general paralysis, and 3 out of 25 cases of other insanities. Dr. Winifred Muirhead (4) did not get a single negative result in 35 cases of general paralysis and 77 cases of other insanities.

In none of these 77 cases was there a lymphocytosis, whereas Williamson describes an increased cell-count in several conditions other than general paralysis.

Noguchi and most of those who have used his test hold that the butyric acid reaction is rarely met with in cases other than the nervous lues, but Mott obtained it in all cases of dementia, whether specific or non-specific.

As regards the after effects of lumbar puncture the records are equally at
variance. Thus, Kissel describes symptoms both in the sane and the insane which appeared 5 to 12 hours after puncture, such as headache, nausea and vomiting on assuming the erect posture, and in some cases complete incapacity for work. Out of 112 cases of insanity, in 48 did pronounced symptoms follow. He advises that not more than 5 c.cm of fluid be withdrawn. Chauffard and Boidin, on the other hand, had only 3 cases of vomiting in a series of 223 punctures, and, apart from slight headache, no other ill effect; and Tissot had similar results, although in many cases of epilepsy as much as 60 c.cm of fluid were withdrawn. In view of these marked divergencies of opinion it is evident that further information is required.

Attention has been directed hitherto mainly to the syphilitic and parasyphilitic affections of the central nervous system, but there is at least a priori reason why the examination
of a fluid which comes into such intimate contact with every part of the cerebral tissue should not yield results of value in other nervous and mental conditions, for we are probably justified in calling the cerebro-spinal fluid the lymph of the brain, receiving the products of its metabolism: it is "the ambient fluid in which exchanges take place between the blood in the capillaries and the neurones" (Mott). In the present research an attempt has been made to obtain such results.

In looking through the literature 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 condition 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. Nevertheless it is very desirable that series of examinations 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 occurring in the brain or its meninges, an excellent example of this being seen in the case of cerebral gumma and abscess described later.

**Historical**

The discovery of the existence of a clear watery fluid which bathes
the brain and spinal cord is usually assigned to Botuguño, but Dr. W. W. Ireland states that in 1742—that is to say twenty-seven years prior to the publication of the treatise of the Italian anatomist Emanuel Swedenborg wrote a description of the fluid. This statement I have been unable to verify, but that it is substantially correct seems probable when one considers the marvellous way in which Swedenborg forestalled many of our modern discoveries in the anatomy and physiology of the nervous system. The first thorough investigation into the physical properties and function of the cerebro-spinal fluid was made by Majendie in 1825, who first gave it the name by which it is now known, and who proved that it was present not only in man but in all mammals, whereas Botuguño, for some unknown reason, failed to demonstrate it in the dog. Majendie recognised that the fluid was free to pass from the skull down the vertebral canal, and he also describes the symptoms which follow the
withdrawal of a large quantity from an animal—"une débilité et une faiblesse générale."
The next advance came in 1858, when Claude Bernard showed that there was a considerable quantity of a substance which reduced Fehling's solution. This substance he considered to be glucose. The fluid was first withdrawn for therapeutic purposes by Quincke in 1891, who introduced the operation of lumbar puncture, hoping that the consequent diminution of intracranial pressure would prove beneficial in such conditions as meningitis and general paralysis, but the method did not realize the expectations entertained of it.
The procedure, therefore, did not come into vogue until the now classical researches of Widal, Sicard, and Ravaut in 1900 showed that cytological changes of the greatest importance from the diagnostic standpoint occurred in the fluid in certain nervous conditions.
In 1903 Castellani demonstrated the
presence of the Trypanosoma gambiense in
the cerebro-spinal fluid of cases of
sleeping sickness.
About this time the practice of producing
spinal analgesia was being introduced,
such drugs as cocaine, stovaine, and
novocaine being injected into the spinal
canal, and anaesthesia of the lower
extremities thus obtained. The addition
of strychnine has made it possible to
extend this method to the upper part of
the body and even the head, as the
strychnine counteracts the tendency to
cardiac and respiratory failure which
the action of the stovaine on the medullary
centres is apt to produce.
The latest discovery regarding the cerebro-
spinal fluid is that of wassermann,
who has shown that in syphilis of the
nervous system, and also in the parasyphtilitic
conditions general paralytic and tabes
dorsalis, the spinal fluid contains a
specific antibody which, by reason of its
power of fixing complement, can be
readily recognised.
The present research was commenced in the Edinburgh Royal Infirmary at the suggestion of Dr. Byron Brainwell, to whom I am much indebted for permission to publish some of his cases, and still more for his continual kind help and encouragement. The cases first examined were chiefly those of tabes dorsalis and general paralysis of the insane, together with a few examples of disseminated sclerosis and cerebral tumour, but the work was continued in the Derby Borough Asylum under Dr. Macphail, where a large variety of forms of insanity were investigated. Altogether 170 punctures were made in 120 patients.

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
reduced Fehling's solution. This substance was considered until recently not to be glucose and from an examination of fluid obtained from meningococci Halliburton concluded that it was pyrocatechin, but he has now returned to the view stated by Claude Bernard in 1858 that the substance is indeed glucose.

The normal fluid is very poor in cellular elements, an occasional lymphocyte being met with, but never a polymorphonuclear cell. In disease, however, the cells may undergo considerable changes. Thus, in acute suppurative meningitis the fluid is found to be swarming with polymorphonuclear leukocytes; it is no longer clear and limpid, but becomes thick, yellow and turbid—indeed it has become converted into a diluted form of pus. Such a polymorphonuclear leukocytosis is always an indication of an acute microbial infection of the brain or its meninges. As recovery sets in the polymorphs are
gradually replaced by lymphocytes, which probably play the part of scavengers, the lymphocytes in turn finally disappear. In the subacute and chronic affections of the meninges, that is to say in syphilis and tuberculosis, 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 fluid contains chlorides, carbonates, phosphates and urea in minute quantities, the principal constituent being sodium chloride, which is present to the extent of 0.6 per cent. These salts probably contain a higher proportion of potassium than the corresponding salts in the blood, for the ash of the brain contains 20 to 30 per cent of potassium as compared with 15 per cent sodium salts. (Geoghan.)

The fluid is faintly alkaline in
reaction, the alkalinity being only half that of the blood (Cavazzani). The alkalinity varies within narrow limits. Scott\(^\text{[17]}\) states that the alkalinity corresponds to 0.1 per cent. sodium hydrate, and gives the following table of the alkalinity in various conditions:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Alkalinity (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Dementia (general paralysis)</td>
<td>0.1076 calculated as Na.011</td>
</tr>
<tr>
<td>General paralysis</td>
<td>0.1056</td>
</tr>
<tr>
<td>Delusional insanity</td>
<td>0.1120</td>
</tr>
</tbody>
</table>

(Fluids obtained by lumbar puncture during life, all about noon.)

The cryoscopic point of the fluid varies from \(-0.51^\circ\) to \(-0.56^\circ\) C (that of the blood being \(-0.56^\circ\) C). Ravaut\(^\text{(18)}\) finds that there is a lowering of the freezing-point in meningitis, both septic and tuberculous, but this method has never attained a position of practical importance.
There is considerable discussion at present as to the occurrence of cholin in the cerebro-spinal fluid. Mott and Halliburton described the presence of considerable quantities of cholin in such conditions as general paralysis where there is great disintegration of the nervous tissue, but Mott is now inclined to the view that these results were partly due to errors in the technique, and partly to the fact that in a number of cases the fluids used were obtained post mortem, and it has been found that such fluids give the cholin reaction a very short time after death.

Hebb, using the method of Halliburton and Rosenheim, obtained cholin-platinum crystals from the cerebro-spinal fluid in cases of cerebral haemorrhage, syringomyelia, and disseminated sclerosis.

As regards other conditions, Donath found that cholin was present in 19 out of 22 cases of epilepsy. But the difficulties of technique are so great, and the pitfalls so numerous, that at
present the matter must be considered sub judice.

It is evident from the foregoing that it is well-nigh impossible to investigate the variations of all the constituents of the cerebro-spinal fluid in health and disease, and attention has been confined in this research to the cytology, the protein content, and the Fehling-reduction.

Cytology

Discussion of methods.

The method employed for enumerating the cells was that of Widal (24), 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, but in a few cases where this would manifestly have underestimated the total number of cells present, only five fields were counted. By counting as many as ten fields the error is not made of choosing a part of the slide where the cells are specially numerous, and thus giving the case a
higher cell-count than it deserves.

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 1901 used the ordinary haemocytological 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, by Fottman and Ayer that when only a few cells are present the error varies from 30 to 90 per cent, and the fluid method of Jones yields no better results.

Proof of accuracy of method used.
As has been pointed out above, 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 present exactly the same clinical symptoms throughout, and if only a short interval of time separate 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 84 cells were present when the fluid was withdrawn five minutes after the patient had had a severe epileptic fit, and the difference between the first two counts in No 19 is capable of a similar explanation, but this case will be dealt with 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, most of the cells being washed off the slide in the process of staining. It was not possible to make a third examination. 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 been 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 know if a similar series of observations with the method of Fuchs and Rosenthal would yield 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 Curves Stewart(27), after 5 cm have been centrifuged for 5 minutes (presumably in an electric centrifuge) not more than 4 cells should be seen
in the field with a magnification of 450 diameters.

Widal (29) considers that a lymphocytosis is present when there are 6 to 10 cells per field under an oil-immersion lens. Easterbrook (29) gives the following figures with an oil-immersion lens: normal 1.2 or 3; slight lymphocytosis 4 to 6; moderate 7 to 20; intense above 20.

I consider that with a magnification of 450 diameters 9 or 10 cells may be present without justifying one in calling the fluid abnormal, but that anything above that number must be regarded as pathological.

Results of Cytological examination.

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—take dorsalis, and general paralysis.

(2) a group comprising the remaining cases.
I. Cytology of the parasyphilitic conditions.

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

Thus Babinski and Pagnolet got a positive reaction in 61 out of 62 cases of tabes, and in 47 cases which showed nothing abnormal except the Argyll-Robertson pupil, a symptom which is now admitted to be strong presumptive evidence of a parasyphilitic as opposed to a purely syphilitic lesion. \(^{(30)}\)
Fraenkel\(^{(31)}\) obtained a positive cytological result in every one of 23 tabetics who were examined.

Riesel\(^{(32)}\) did the same in 58 cases of general paralysis.

Régna\(^{(33)}\) states that a lymphocytosis occurs in every case of general paralysis at some stage of the disease, and that it occurs in no other variety of insanity except with a history of syphilis, and even then it is discrete—only a few cells being present. With this latter statement I shall have occasion to join issue presently.

Edwin Bromwell\(^{(34)}\) describes a case of juvenile general paralysis in a boy aged 15, in which there was a marked lymphocytosis.

In the great majority of cases, therefore, the syphilitic and para-syphilitic lesions of the central nervous system are accompanied by a lymphocytosis in the cerebro-spinal fluid.

These conclusions are fully supported
by my own results. From an inspection of Table II it will be seen that in every case of general paralysis, the lymphocytoysis was well marked, in no instance falling below 40, and in one remarkable case reaching the unprecedented number of 3400.

In only two cases of tubers 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 was never higher than 14. All the other cases showed a well marked lymphocytoysis.

2. Cytology of the ordinary insanities

Turning now to the second group, which to me is by far the more interesting, one is confronted with a much more difficult problem, and it is here that the results of other observers are of great
interest. The most diverse opinions exist as to the occurrence of a cerebro-spinal lymphocytosis in conditions other than the parasyphilitic affections. (It should be mentioned that tubercular meningitis is not under consideration at present; in that condition a lymphocytosis is the rule.) Dr. Winifred Muirhead \(^{(35)}\) considers that a cellular increase is the most constant change in general paralysis, and in 77 cases of other insanities she did not obtain a single positive result.

Foucault, as mentioned above, declares in the most categorical way that a lymphocytosis occurs in no other form of insanity unless with a history of syphilis.

Williamson \(^{(36)}\), on the other hand, got a high cell-count in 6 cases of insanity divided between epileptic and acute mania. Curves Stewart \(^{(37)}\): "In mental diseases cytological examination of the cerebro-spinal fluid yields negative results."

Römheld \(^{(38)}\) reports a case of diphtheritic pseudo-tubes in which a "moderate lymphocytosis" was present.
In ordinary disease, as distinguished from insanity, an increased cell-count has been described in a number of conditions.

Thus Otto Rehm(39) obtained a positive result in one case of chronic alcoholism with probable syphilitic infection, two of syphilitic brain disease, two of syphilitic arterial disease, two of hysteria, and two of imbecility.

Curves Stewart(40) did the same in gumma of the spinal cord, endothelium of the cord, gumma of crus cerebri, glioma of corona radiata, Landriy's paralysis, tubercular meningitis and a number of syphilitic nervous affections.

Cerebral tumours on the surface produce a lymphocytosis, owing probably to involvement of the membranes, but it is difficult to understand a case mentioned by Curves Stewart(41) in which a glioma of the centrum ovale was accompanied by a marked cellular increase.

A lymphocytosis has been noted in mumps and herpes zoster, in which conditions, as Herzbacher(42) points out,
there is no question of meningeal irritation.

The consensus of opinion appears, therefore, to be 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. As far as I have been able to ascertain, Williamson (45) is the only observer who has reported a lymphocytosis in the ordinary insanities, but the details which he gives both as regards the number of cells found and the conditions in which the increase occurred are so meagre, that a discussion of these cases is not possible.

To these conclusions my own results are strongly opposed. From Table II it will be seen that out of a series of 117 cases, in 71 was the cell-count below ten, whilst in 46 was it above ten and therefore to be considered pathological. Of these 46 cases are subtracted 10 cases of tabes, 1 of tabospasticis, 10 of general paralysis, and 1 of
acute suppurative meningitis, there is left a group of 14 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 aneurism, which was definitely syphilitic. Of these 14 cases, those of aneurism, 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 of excitement in which, judging from Williamson's observations, one would expect a slight cellular increase.

There are two cases of congenital imbecility: in one the count was 25, in the other it was 18, and 19 on a subsequent occasion. Otto Rehm, as mentioned above, obtained a positive result in two cases of imbecility. The
occurrence of a definite lymphocytosis in these two cases is of interest in connection with the series of cases of dementia praecox to be described later.

Of the three cases of cerebral tumour, one was a gumma producing a lymphocytosis of 21; under antisyphilitic 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 of 110, but it presented some features of such peculiar interest that it will be dealt with more fully later.

In both these cases, therefore, one has to deal with a syphilitic infection of the brain.

In the third case, however, there was no history of syphilis. 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-cell sarcoma, and yet the cell-count reached the enormous number of 1630. The importance of this case lies in the demonstration which it provides that a very marked cerebro-spinal lymphocytosis may be present without either a syphilitic or a tuberculous process being the causal factor.

Of the five cases of epileptic insanity in which a lymphocytosis was observed, two had between 20 and 40 cells, one having 50 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 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 well 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 less than five minutes after the patient had taken a fit. The counts on three subsequent occasions were 14, 23 and 38.

The third case was altogether exceptional, and will be discussed later. Suffice it to say that on four occasions a marked cellular increase was present, the last being the highest with a count of 80. Out of a series, therefore, of 15 cases of epileptic insanity, in 5 cases was there a well-marked increase in the cell content, this increase being present, although varying in extent, on the different occasions on which the fluids were examined. In none of these cases was excitement a prominent symptom, and the case in which the largest cell-count occurred was one of the quietest patients in the institution. It is only fair to mention, however, that this was the case
in which the fluid was withdrawn immediately after a fit.

A difficult group of cases.

There are now left ten cases of dementia praecox 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 praecox 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 praecox, but I do not wish to imply that they all presented perfect clinical pictures of the disease. On the other hand it may be urged that seldom indeed does one find a case which does so. Rather have I classed them thus because, with one exception, they are all young adults, the symptoms have a vagueness which one is only too apt to associate with dementia praecox, and one of the chief features has been 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 emphasize 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 neuronal metabolism. 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. 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 call 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 was not regarded as a definite entity at all. I am convinced that this process will be extended to other mental diseases, and until that is done clear thinking in psychiatry is impossible.

Now the discovery of the presence of a definite constant pathological change in the cerebro-spinal fluid in a group of cases presenting similar clinical symptoms is, to my mind, a step in the right direction.

According to Stoddart (44), dementia praecox may be regarded from one point of view as a failure in evolution, and he points out certain physical similarities between that condition and idiocy and imbecility. (It will be remembered that in two cases of imbecility there was a moderate lymphocytosis.) In every one of my series of ten cases one got the impression that there was a congenital element present, more marked in some cases.
than in others.
A few of the cases could not be better described than by saying that they were "soft"; they managed well enough under the regular regime of the institution, but were quite unable to hold their own in the struggle for existence in the outside world. For instance one patient, whose brother is a distinguished graduate of Edinburgh University, was found on admission to be in a condition of indescribable filth, owing to his not having had his clothes off for a year, and yet he has been perfectly rational and a willing worker ever since, although always a trifle "soft", and with deficient emotional reaction. In his case there were 471 cells per field. Under ordinary circumstances one would have been astonished to get such a result, but once I came to recognise the family relationship between the cases, I found that I was able to forecast with some degree of accuracy the result of the lumbar puncture, and I chose this case because I was almost certain that it would provide a positive result.
These cases are 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, aged 21 years. Paternal aunt was insane. Admitted to the Derby Borough Asylum in October 1909. For a year previously she had been losing energy and interest in life, would sit still for hours gazing in front of her, and was on the whole depressed. On admission she was dull, stupid and apathetic, mentation slow - a question taking a long time to reach her understanding and regarded her question with a dull meaningless gaze. She would often repeat a question, merely with a change in the personal pronoun. When placed in one position she would remain thus indefinitely, but there was no catatonic rigidity of the limbs. No delusions or hallucinations. Habits wet and dirty. She was in poor condition, but without any active physical disease. She gradually became brighter, habits improved, and she began to employ herself, but is now in status quo. She is at present in a
childish, almost mindless condition, with complete loss of memory — she cannot tell my name, nor whether she has had dinner or not. There is not a trace of emotional response; thus, when told of the death of her mother, to whom she was very attached, she showed no sorrow or grief. Joy is unknown to her, as well as sorrow.

The cell count on three different occasions was 31. 54. 26. The Koguchi reaction was positive but faint. The ammonium sulphate test was positive with a dilution of 1 in 5.

Case 2. W.M., male, aged 25 years. A step-sister is insane. Patient was admitted to the Derby Borough Asylum in July 1910. He is said to have been rather "soft" and below the average intelligence all his life, but his occupation being that of bricklayer's labourer, he managed to get along until a few weeks before admission, when he became very stupid and confused, and commenced to ramble in his talk. This was his condition on admission, he understood little of what was said to him, but asserted in a facile
way to any suggestions that were made. Habits wet and dirty. No definite physical disease. He remained in this dull, confused condition for about a year, and then gradually improved to a certain extent. At present he is weak-minded and facile, and seems incapable of experiencing joy or sorrow. The cell count on two occasions was 121 and 86. Both the Kaguchi and Ammonium sulphate tests were negative.

Case 3. H. M., male, aged 21 years. No hereditary predisposition to insanity ascertained. The difficulty about classing this patient as a case of dementia praecox lies in the fact that he has had two previous attacks from which he has recovered, but in spite of that there is little doubt in my mind that he is an example of this disease. Little was known concerning his previous history except that this was his third attack. 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. There was nothing abnormal in his physical condition. As time went on he became more excited, and began to go in for attitudinising; he also began to develop catatonic symptoms thus, when his arm was raised above his head he would keep it in that position for a minute or more. He showed, in addition, symptoms of negativism. After nine months the severity of these symptoms showed signs of subsiding; and he is now quiet and fairly rational, but is still childish and simple, with impaired memory. I should not say that he is particularly lacking in emotional feeling.

The cell-count was 10, Kugel's reaction was doubtful, and the ammonium sulphate test gave a ring with the undiluted fluid.

Case 4: E. B., male, 30 years. A brother is insane. Patient was a sharp and clever youth up to the age of seventeen, when he began to degenerate both mentally and physically. At last he...
was removed to an asylum, where he remained for two years. He was discharged as recovered, but after being at home for some time he again began to get into bad ways, became moody and irritable, and refused to live with the rest of the family. He was admitted to the Derby Borough Asylum in January 1910, and it was then found that he had not had his clothes off for a year. When questioned as to the reason for this he said that he just got into the way of not undressing. He seemed to have little hold upon life, and nothing gave him any pleasure or amusement. He was in poor condition, but without any actual disease. He has improved considerably, and is now able to converse rationally and to employ himself usefully, but he is still simple, facile and childish. His cell count was 41, and both the Noguchi and ammonium sulphate tests were negative.

Case 5. A. M., male, age 21 years. No hereditary predisposition to insanity ascertained. A cattle-drover by trade.
but has always been of a rather weak type. He was admitted to the Derby Borough Asylum in February 1909 in a confused condition, staring vacantly about him, rambling and incoherent in his talk, and expressing delusions of persecution. He remained in this condition for rather more than a year, and then began to get more rational. He can now talk coherently, and works in a mechanical way, but he is facile and simple-minded.

This case certainly does not conform to the textbook descriptions of dementia praecox, but on the other hand it bears a distinct resemblance to other cases in this series, and the impression left in my mind—an impression for which it may be difficult to give adequate reasons—is that it ought to be placed along with the others in this class.

The cell count was 20, the Koguchi reaction negative, the ammonium sulphate test positive with the undiluted fluid, and there was very feeble reduction of Fehling's solution.
Case 6. A.K.W., female, aged 33 years. Father was insane. She has always been of a neurotic, highly-strung, religious temperament. As the result of the severe strain of nursing a mental case for eighteen months, she broke down in health, and soon showed mental symptoms. She became rambling, foolish, unduly sentimental and religious, and finally grew extremely violent, and struggled, fought and screamed. On admission (January, 1911) she was restless, talkative and excited, but her symptoms had a distinct suggestion of hysteria: thus, she gave me a wonderful imitation of an epileptic fit, and then commenced to bark like a dog. She has grown worse rather than better, and the motor symptoms have now assumed the catatonic type; when asked a question she always repeats it in the same form, she will stand in one position and make absurd and bizarre gestures for hours, and shows negativism in a marked form, doing exactly the opposite to what she is asked to do, and on one or two occasions refusing her food for days and having to be tube-fed.
in consequence. It is difficult to say with certainty whether or not her capacity for emotional reaction is affected. The cell-count was 70. Both the Noguchi and the ammonium sulphate tests were negative, and Hekling-reduction was very slight.

Case 7. F. H., female, aged 25 years. Admitted to the Derby Borough Asylum in April 1909. Paternal aunt was insane, and paternal grand-aunt committed suicide. A few months before admission she gave birth to an illegitimate child, and soon became depressed, morose, suspicious and delusional. Since she has been here she has been sullen and reserved at times, with delusions of persecution, at other times noisy, excited and abusive. She has been steadily drifting into dementia, and the lack of emotional reaction is very marked in her case. I did not see her in the earlier part of her illness, and can give no account of any motor symptoms which may then have been observable.
The cell-count was 19, and both the Noguchi and ammonium sulphate tests were negative.

Case 8. J. P., male, aged 34 years. Admitted to the Derby Borough Asylum in November 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 Noguchi and ammonium sulphate tests were negative.

Case 9. R. J., male, aged 35 years, but was only 19 years old when admitted. A brother was insane, as was a relative on the mother's side. Before admission he was dull, depressed and exclusive, shutting himself up and refusing to associate with other boys. On admission he is said to have been dull and lethargic, furtive.
and suspicious, and he was diagnosed as 'melancholia'. 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 Noguchi and ammonium sulphate tests were negative.

Case 10. J.H., male, aged 42 years, but was only 23 years old on admission. None of his relatives were insane, but some other members of his family were very peculiar and eccentric in their behaviour. He used to be a medical student at Edinburgh University, where he was keen on his work, in addition to being a fine athlete and a member of the University cricket XI. He broke down (under the strain of work it was said) and was admitted to the Derby Borough Asylum 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, gazing up to the sky for long periods, and gradually becoming more and more demented. He is now profoundly demented, and is the most incoherent person I have ever met; there is no connection between the different parts of his sentences, and his speech runs something in this fashion: - "He went up the black house is running very cold yesterday."

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 to place her in the class just described; she is certainly not a typical case of melancholia. The patient is a woman of 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 - in short, there
was loss of emotional reaction. For some time after admission she remained dull and apathetic, 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) she appears to be incapable of experiencing any acute emotion. I examined her cerebro-spinal fluid before I had had any experience of this class of case, and my astonishment was great when I discovered a lymphocytosis of 103. It became still greater when on a subsequent examination a few months later I found the cell-count to be 340. On a third examination it was 120. The protein content of the fluid was increased.

It is difficult to know what to say about this case. There seems to be nothing special the matter with her, her nervous system appears to be normal, she is rational and coherent and quite free from delusions, and, apart from a certain listlessness and lethargy which might easily be met with in persons who had never seen the inside
of an asylum, there is little to find fault with in her mental processes. The task of explaining this marked and constant lymphocytosis is certainly a difficult one.

Summary of Cytological Results.

To briefly summarise the results obtained from an investigation into the cytology of the cerebro-spinal fluid, the following points are to be noted:

1. For practical purposes of comparison between different cases the field method of Widal is, on the whole, satisfactory.
2. It is desirable to have records of the condition of the cerebro-spinal fluid of the same case on different occasions, in order partly to judge of the reliability of the technique used, partly to determine if changes occur in the fluid under normal and pathological conditions.
3. The results obtained in the syphilitic conditions were in accordance with those of other observers. In every case of general paralysis there was a marked cellular
increase, and in only two cases of
sales was it not well marked.

4. In one case of non-specific cerebral
tumour there was an enormous lympho-
cytosis. Therefore a very high cell-count
does not necessarily imply the presence
of nervous lues, as has been considered
hitherto.

5. Emotional excitement seems to have
no effect 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.

As has already been mentioned, the cerebro-spinal fluid contains only a trace of protein in the form of serum globulin and albuminose, the total amounting to about 0.03 per cent. Albumen is never present under normal conditions. In those conditions in which the cells are increased in number, that is to say, in the acute and chronic inflammatory conditions of the brain and its meninges, the protein content is increased. This change is in great part due to the globulin, but albumen and nucleo-protein may also be present. The greater part of the protein is coagulated between 73° and 80° C. The protein increase bears, as a rule, some relation to the cellular increase.
but that this is by no means always the case will be seen later.

In the estimation of the protein content of the cerebro-spinal fluid many methods have been used, but of none of them can it be said that they have proved altogether satisfactory.

If a very strong reagent, such as concentrated nitric acid, be used, the trace of globulin which is normally present in the fluid will probably give a positive reaction in every case.

On the other hand, the reaction must be a fairly delicate one, else a slight pathological increase will be missed. A test, therefore, which is only positive in the presence of such large quantities of protein as are met with in general paralysis is not of much value for estimating the slighter changes which may occur in the other insanities.

Of the methods which have been used the following may be mentioned:
(1) Guillain (45) precipitated the globulin by half-saturating the fluid with magnesium sulphate, and then boiled the clear fluid; if a precipitate appeared it was taken to indicate the presence of albumen, and was said to be pathognomonic of general paralysis. This method was tried by the present writer in a number of cases, and found to be unsatisfactory.

(2) Kissel (46) added an equal quantity of saturated ammonium sulphate solution to the fluid; an opalescence was taken to indicate a positive result.

(3) Binical used a saturated solution of zinc sulphate.

None of these methods, however, are found even by their authors to give satisfactory or reliable results.

The difficulty is to be certain when the protein present passes the limits of the normal, and before that can be decided it is necessary to be quite certain as to what the limits of the normal are. It cannot be said that this question has been satisfactorily answered.
up to the present, and this is one of the points to which I have directed special attention.

Another important point is to have a simple means by which the exact amount of protein present may be estimated. It is not difficult to determine whether or not there is a marked excess, but we ought to have a quantitative comparison of the amounts present in cases which show only a slight increase. Given such a method, we should be able to compare fluctuations which occurred in the same case, in exactly the same way as has already been done in the case of the cellular elements.

In the present research two additional methods have been used, and have given great satisfaction; they are the butyric acid test of Hogeichi and the ammonium sulphate ring test of Jones and Ross. Before applying either test care must be taken that the fluid is perfectly free from blood. Both of these
Tests depend upon precipitation of the globulin present, which constitutes the main bulk of the protein, at least in general paralysis. As Jones points out, this globulin is in the form of a eu-globulin, and has peculiar interest insomuch as it is probably the active principle in the Wassermann reaction.

Noguchi's test consists in the addition of 5 c.c.m. of 10 per cent nitric acid to 2 c.c.m. of cerebro-spinal fluid and the application of heat for a few seconds, 1 c.c.m. of 4 per cent solution of sodium hydroxide 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 tuberculous meningitis, although a haze may be met with in normal fluids.

In the Ross-Jones (17) reaction 1 c.c.m. of cerebro-spinal fluid is run on to the
surface of 2 c.cm of a saturated solution of ammonium sulphate in the same way as is done in the nitric acid test for albumen in the urine. 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.

It is here, however, that difficulties arise. In the first place the time in which the ring appears varies considerably in different cases. Then much depends upon the background and the illumination used. A faint ring may be completely missed if proper precautions are not adopted. Where, as in the present instance, a quantitative estimation for comparative purposes is being attempted, it is essential that the conditions under which the test is made be always identical. It is best to use indirect illumination from a powerful electric lamp, the test-tube being held against a black background. As regards the time, the test was held to be positive if the ring
appeared within five minutes.

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 for quantitative estimation as any that has been hitherto used.

In the earlier cases the test was not carried out in the cold; the ammonium sulphate was dissolved in boiling water till a saturated solution was obtained, and the cerebro-spinal fluid was then run on to the surface of this hot solution, with the result that a ring was obtained in the normal, the reaction being as a rule three or four times as delicate as the cold test, but readings taken on different occasions were found not to be so uniform. The first cases of the series were examined before the ammonium sulphate ring test had been described, and a note was merely made as to the presence or absence of excess of protein, this being roughly estimated by heating the fluid, the normal fluid
giving only a slight opalescence, whereas in the case of excess of protein there was a distinct cloudiness.

As in the case of the cell-count, so now in the estimation of the protein content, the accuracy and reliability of a method may be checked by making repeated observations in the same case, always provided that the case in question presents the same clinical features throughout.

This has been done in the case of the ammonium sulphate test, and the results are embodied in Table III. From this table it will be seen that in a considerable number of cases the fluid was tested on two occasions, in three cases on three occasions, and in one case as many as six times.

Sometimes the result was rather doubtful, it being difficult to decide whether a really satisfactory ring had appeared within five minutes. In such cases a doubtful reaction was taken as being negative.
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, accurate and reliable means of estimating the protein content.

In only one case was the difference marked, and that was a case of acute mania (No. 4) in which a positive reaction was obtained with a dilution of 1 in 4, then it dropped to 1 in 1, but had risen again on the third occasion to 1 in 4. In the other cases the variations were negligible.

Results.

It is generally admitted that an increase in the protein content of the cerebro-spinal fluid is one of the most constant features of tabes dorsalis and general paralysis.

Thus Cornell (48) obtained an increase of albumen in all the cases of general paralysis which he examined.

Hamilton Marr (49) records similar results.
Pigna \(^{(50)}\) states that serum albumen is always present in general paralysis, and that the percentage of serum globulin is high.

Jones \(^{(51)}\) finds that in paresis the protein content is often increased four or five-fold; albumen is constantly present, but the main bulk is globulin.

Winifred Muirhead \(^{(53)}\) using the Hoquechi and Ross-Jones tests obtained a positive result in 33 out of 35 cases of general paralysis and a partial reaction in the remaining 2 cases.

Williamson \(^{(53)}\) got a positive Hoquechi reaction in 20 out of 21 cases of general paralysis, in 2 out of 4 cases of tabo-paresis, and in 4 out of 5 cases of tabes.

With these observations my own are in perfect accord.

Thus, the Hoquechi test was positive in every case of tabes, tabo-paresis and general paralysis that was examined.

The ammonium sulphate test gave
exactly the same results.
Not only was this test positive, but in almost every case the increase in the protein content was very marked, as was shown by the promptitude with which the ring appeared, and the degree of dilution with which it could still be obtained. Thus in one case of general paralysis and in one case of tuberculous arthritis there was so great a amount of globulin present that a distinct reaction was obtained when the fluid was diluted 12 times. On the other hand one typical case of general paralysis only gave a positive reaction with a dilution of 1 in 2, and lost it when a higher dilution was used. From the table it will be seen that in seven other cases of insanity a positive result was obtained with a similar dilution; repeated examination of this case was accordingly carried out. On five occasions a similar result was obtained, but on a sixth occasion (which came in the middle of the series), a ring was obtained with a dilution of 1 in 4. The lymphocytes
in this case was well marked. With this exception, however, the test gave in every case an instant and clear indication of the presence of a large amount of protein. It is with the protein, therefore, as it was with the cells, there being little room for difference of opinion in so far as the para- or syphilitic conditions are concerned.

It is otherwise, however, with the non-syphilitic diseases. The general teaching used to be that there is no increase of protein content in these conditions. Even so lately as 1909 we have the following statement from Jones:

"The Noguchi and ammonium sulphate tests are always negative in all other forms of mental disease."

A number of observers, however, have recorded the presence of increase of albumen or globulin (the method of detection being in some cases not specified), but of course it does not follow that the two above-named tests would have proved positive in these cases.
Regna (55) found that there was a trace of albumen in seven cases of senile dementia in which arteriosclerosis was present. Hamilton Marr (56) states that serum-albumen, which in general paralysis he found varied from 0.05 to 0.4 per cent occurs in many forms of insanity; he found it constant in chronic alcoholism, and occasional in epilepsy and organic brain disease. He considers that its persistence renders recovery from the mental condition unlikely.

Niel (57) obtained an increase of albumen in one case of catatonia, two senile dementos, one epileptic, one arteriosclerotic dement, and one case of brain syphilis.

Easterbrook (58) gives the following list of conditions, in addition to general paralysis and tabes, in which an excess of albumen has been found: apoplexy, meningitis, secondary syphilis, syphilitic hemiplegia, facial erysipelas, epilepsy, catatonia, senile dementia and arteriosclerosis.

Evidently, then, it cannot be maintained that an increase of protein content is confined to general paralysis and tabes.
but it remains to be seen whether the butyric acid and ammonium sulphate tests will prove positive in other conditions than these.

In the case of the Poguchi test it will be seen from Table II that a positive or doubtful reaction was obtained in 1 case of pituitary tumour, in 2 out of 10 cases of dementia praecox, in 4 out of 15 cases of epilepsy, 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 praecox group. The pituitary tumour was of a definitely non-syphilitic character. In 81 other cases the test was negative.

It is evident, therefore, that the en-globulin, which is said to be indicated by a positive result, cannot be regarded as being characteristic of the parasyphtilitic conditions, although in them it is certainly more constant and more marked. What its presence means in such conditions as epilepsy and dementia praecox it is difficult at present to say.
but it remains to be seen whether the butyric acid and ammonium sulphate tests will prove positive in other conditions than these.

In the case of the Noguchi test it will be seen from Table V that a positive or doubtful reaction was obtained in 1 case of pituitary tumour, in 2 out of 10 cases of dementia praecox, in 4 out of 15 cases of epilepsy, 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 praecox group. The pituitary tumour was of a definitely non-syphilitic character. In 81 other cases the test was negative.

It is evident, therefore, that the eu-globulin which is said to be indicated by a positive result, cannot be regarded as being characteristic of the parasyphtilic conditions, although in them it is certainly more constant and more marked. What its presence means in such conditions as epilepsy and dementia praecox it is difficult at present to say.
Turning now to the ammonium sulphate test we find that the reaction was positive in 45 out of 86 cases. Subtracting the 9 cases of tabes and general paralysis, we are left with 36 positive results in cases without any definite evidence or history of syphilis. This large number is, in my opinion, to be explained as follows.

The ammonium sulphate test may be done in one of two ways. The cerebro-spinal fluid may be poured on to the surface of the sulphate solution, and the white ring at once looked for. If the case be one of general paralysis, the ring will immediately appear, and will be so definite that it cannot be possibly missed. If, on the other hand, the fluid which is being tested contains only a slight increase of protein, then no ring will be apparent at first, but if the tube be put aside and looked at within five minutes, powerful indirect illumination being used, and a black background placed behind the tube, then careful examination may show a
faint but still distinctly ring to be present. If these precautions be adopted, such a result will be obtained in many cases which would otherwise have been called negative. The question comes to be - Does such a result indicate a pathological change? I am inclined to think not, for I have obtained a positive reaction in a few cases which appeared to be perfectly healthy from the nervous and mental point of view. I should say that a faint reaction with the undiluted fluid, which is lost when a dilution of 1 in 2 is employed, is not to be regarded as indicative of disease.

That the foregoing explanation is correct appears to me probable from the fact that in the earlier cases of the series I seldom obtained a positive reaction, but when I began to adopt the precautions mentioned above, I found that a faint ring was much more commonly met with. Out of the 36 cases at present under consideration 26 gave a positive reaction only when the undiluted cerebro-spinal
fluid was used, quite failing to give it even with a dilution in 1 in 2, by which I mean one part of the fluid to one part of water. This leaves only 10 cases which gave a distinctly pathological result. Three cases being analysed stand as follows:

one case of pituitary tumour with an enormous increase in the globulin;
one case of acute mania: in this case a reaction was twice obtained only with the undiluted fluid, but on a third occasion it gave it with a dilution of 1 in 4;
one case of melancholia: this was the case already described which closely resembled dementia praecox, and the same result was obtained on two occasions;
one case of dementia praecox;
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 occurred to give positive results with the butyric acid and ammonium sulphate tests.

As regards the relation between the two tests it may be noted:
1. That 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.

As to the somewhat vexed question of the relation between cell count and protein content, the following facts emerge:
1. A positive Noguchi was only once unaccompanied by a lymphocytosis: this was a case of epilepsy in which there was only one cell per field, although, in addition to the Noguchi, the ammonium sulphate test was positive with a dilution.
of 1 in 2. Only one examination was possible, and it may be that the technique was at fault.

2. A positive ammonium sulphate test with a dilution of 1 in 2 and upwards was only once met with in a case which showed no lymphocytosis; this was a case of acute mania in which the test was positive with a dilution of 1 in 4. But on two other occasions it was only positive when the undiluted fluid was used.

3. In 17 cases a lymphocytosis was present without being accompanied by both the Ho- guchi and ammonium sulphate reactions (Table VI). Only in No 5 was there the suspicion of a positive Höguchi, and No 3 was the only case in which the ammonium sulphate test was positive with a dilution of 1 in 2.

Briefly then, when the Höguchi test is positive, and when the ammonium sulphate ring is given with a dilution of 1 in 2 and upwards, a lymphocytosis is almost invariably met with. On the other hand,
a well-marked lymphocytosis may be present, and yet both the protein tests may be negative.

**Fehling-reduction.**

It has been seen that the opinion of many observers on the subjects of cytology and protein content has been remarkable for its diversity, and the same is true regarding the Fehling-reducing substance present in the cerebro-spinal fluid. The teaching usually contained in the books is that the only conditions in which there is a marked change in this substance are diabetes, acute meningitis, and general paralysis. In diabetes it is greatly increased, in acute meningitis and general paralysis it is greatly diminished or altogether absent.

Williamson, as mentioned earlier, found that reduction was absent in 16 out of 23 cases of general paralysis, 5 out of 25 cases of other insanities, 3 out of 6
cases of syphilis, and 1 case of pernicious anaemia. Winifred Muirhead, on the other hand, did not get a single negative result in 35 cases of general paralysis and 77 cases of other insanities.

There are equal differences of opinion regarding the nature of the substance. At first Claude Bernard taught that it was glucose. Then Halliburton, from his work on the fluid from meningocoele, declared it to be pyrocatechin. Finally, the original view is again gaining ground, and Halliburton himself is of opinion that the substance is glucose.

Mott gives the following reasons for considering that the substance is glucose:
(1) it gives with phenylhydrazine the crystals of ovazone which melt at from 205° to 206°;
(2) it is dextro-rotatory;
(3) by the yeast fermentation test it yields carbon dioxide.

Little importance is attached as a rule to the glucose in the cerebro-spinal fluid, and it is seldom that accurate
estimations are made. Recent researches by Mott (59) however, seem to indicate that this fluid may be of vital importance in the economy of the central nervous system. He is of opinion that the cerebro-spinal fluid plays the part of lymph to the brain, and that the sugar which it contains is being conveyed from the blood to the neuronic elements. The fluid itself probably does not contain a glycolytic ferment, but such a ferment may be produced by the ganglion cells, and the sugar thus converted into neural energy. If this hypothesis prove correct, it at once becomes evident that a diminution of the amount of sugar present may be of the gravest import, for the nerve cells would then be unable to obtain a substance which is essential for their healthy functioning.

The amount of glucose varies from 1.2 to 2.5 per 1000.

Mott gives the following table, from which it will be seen that in every case of dementia praecox the quantity of glucose was lower than in any of the other conditions.
Reducing substance in cerebro-spinal fluid.
Male. Old hemiplegia, syphilis.
Post mortem 0.212 calculated in terms of glucose.

<table>
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<tr>
<th></th>
<th>0.186</th>
<th>0.171</th>
<th>0.147</th>
<th>0.146</th>
<th>0.133</th>
<th>0.127</th>
<th>0.126</th>
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<tbody>
<tr>
<td>General paralysis</td>
<td></td>
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<td>Neurosis</td>
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<tr>
<td>Female. Dementia praecox</td>
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<td>0.146</td>
<td>0.133</td>
<td>0.127</td>
<td>0.126</td>
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</tr>
</tbody>
</table>

(Fluids obtained by lumbar puncture during life.)

My own results agree with those of Muirhead in that I have not come across a single case in which the Feulgen-reduction was entirely absent. I have not made an accurate quantitative estimation, but have found that the amount of glucose fluctuates in different conditions, although not in a constant enough way to enable me to draw any definite conclusions. The reduction was feeble in two cases of acute mania, one case of congenital imbecility, two cases of dementia praecox, 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 appeared to be present in normal amount with the exception of two cases of diabetes in which a very large quantity of glucose was present. In one of these cases di-acetic acid was readily demonstrated; the patient died shortly afterwards of diabetic coma.

After-effects.

In no point in the examination of the cerebro-spinal fluid is there greater diversity of opinion than as regards the after-effects of lumbar puncture. The statements met with in the literature flatly contradict each other. Williamson (60) says: "in no instance have I seen any ill-effects on a patient from the withdrawal of the fluid."

As was mentioned at the beginning of this paper, 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.

Pissot, on the other hand, had a very different experience, for he 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 also records that seven doctors were lumbar punctured; of these, only one remained all right, the other six suffering from headache, nausea and vomiting coming on a few hours later. In one case the symptoms lasted for more than a week.

Babcock (61), who withdrew huge quantities of cerebro-spinal fluid in the hope of improving the condition in general paralysis, says that in many cases the headache was so excruciating as to be almost unbearable, being likened to a nail driven into the skull.
D. A. (62) stated that the headache which follows lumbar puncture is occasionally psychical or reflex, for it occurred in one case where no fluid was withdrawn.

What, then, is the explanation of these great differences of opinion? I think that there are two main causes.

1. The type of disease affects the after-results. The one condition in which evil effects never seem to occur is general paralysis. Niel noted this fact in his series of 112 cases, and in my own work I have not met with a single case of general paralysis in which there were any after-effects. Now, if a series of general paralytics be lumbar punctured, there may be no subsequent symptoms to note, whereas if the series contain few or no paralytics a very different state of affairs may result. The immunity of the general paralytic is probably due to the very large amount of cerebro-spinal fluid that is present, the withdrawal of five or six cubic centimetres not producing any appreciable difference.

2. The time that the patient stays in
bed after the puncture is of the greatest importance, but this is not given in detail in the reports of cases in which unpleasant after-effects occurred. Without such information, however, it is impossible to make comparisons between the results of different observers. The patients may have been in bed in hospital, not getting up for some weeks after the withdrawal of the fluid; or they may have got up the same or the next day.

A very curious example of an unpleasant after-effect is that described by Schard [53]. The case was one of suspected syphilis, but no lymphocytosis was discovered. Five days later pain was felt in the lumbar region, and a herpetic eruption four inches in length appeared, extending downwards and outwards from the lower end of the sacrum.

My own results correspond with those of Nissel. I am strongly opposed to those who say that lumbar puncture is
a trivial procedure which is hardly ever followed by unpleasant symptoms. Of the 120 patients who were punctured, 25 suffered so severely as to be deemed worthy of inclusion in Table VII. Many others suffered transitory discomfort such as slight headache, but in the cases shown in the table the symptoms were really severe.

The cases which were examined in the Edinburgh Royal Infirmary were naturally confined to bed, and were for the most part cases of general paralysis and tabes dorsalis, and no case showed any unpleasant after-effects.

The cases examined in the Derby Borough Asylum were usually kept in bed for 36 hours, sometimes for 48 hours, and sometimes for still longer. The symptoms usually appeared soon after getting up, and sometimes the moment the erect posture was assumed. In some cases, on the other hand, no symptoms appeared for 24 or 48 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 case 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.

In every case the symptoms at once disappeared on assuming the recumbent posture. There is one exception to this statement, however, and that is to 20, who was kept in bed for three days because he did not wish to get up, although he felt quite well, and on the third day he vomited several times.

It is difficult to formulate any theory which will explain this strange delay in the onset of the symptoms, for if the headache and nausea which often came on when the erect posture was assumed
were due to diminished intracranial pressure, then how could these symptoms be delayed in some cases for 48 hours?

**Blood Pressure.**

Many of the symptoms produced by withdrawal of the cerebro-spinal fluid were medullary in type and it occurred to me that the diminution of the intracranial pressure might affect other centres in the bulb, such as the vaes-motor centre. I accordingly made a series of observations upon the blood pressure in seven cases before and after lumbar puncture. These cases included some in which on a previous occasion severe symptoms had occurred.

The first observation was made just before lumbar puncture was performed. A reading was then taken five or ten minutes later, and in some cases a third one was made after a few hours. In each case the instrument used was Martin's modification of the Riva-Rocci sphygmomanometer.
Although the general tendency appeared to be for the pressure to fall slightly, yet in some cases it made a corresponding rise. The conclusion to be drawn, therefore, is that the vasomotor centre is not affected by the withdrawal of a small amount of cerebro-spinal fluid. It is possible, of course, that had the patients been made to get up immediately after lumbar puncture, a more marked fall in the blood pressure might have been observed, but I did not consider it justifiable to do this.

In Table VIII is given the blood pressure in millimetres of mercury, the first reading being taken immediately before lumbar puncture, the second about ten minutes later.

**Blood Examination**

In some conditions, such as meningitis, in which the cerebro-spinal cells are affected, there are corresponding changes in the blood. That is to say, the infection, although localised to the central nervous
system, yet affects the blood which flows through that system. It would be interesting to know in how many conditions this may occur. There is said by Borell \(^{(69)}\) to be some correlation in general paralysis between spinal and haemic leucocytosis, applying mainly to the mononuclears, but including also the polymorphs, especially after a seizure. I have not worked at this subject in general paralysis, but it occurred to me that a similar correlation might exist in the group of ten cases with symptoms resembling those of dementia praecox. The results of this investigation are given in Table IX. It will be seen that there was no definite relation between the leucocytosis in the spinal and haemic fluids. In no case was there a haemic leucocytosis, and the only peculiarity about the differential count was the low percentage of polymorphs in some of the cases, but this was merely in accordance with the well known fact that as a case drifts into dementia the polymorphous cells tend to decrease in
number. The cell-count in the case of melancholia which presented the large cerebro-spinal lymphocytosis was also quite normal.

**Some Cases in which the Cerebro-spinal Fluid presented features of peculiar interest.**

In the course of this paper a number of cases have been encountered in which the cerebro-spinal fluid showed features of special interest. It was not possible to discuss them fully at the time, and I now propose to give a more detailed account of these cases.

**Case I. Cerebral Gumma and Cerebral Abscess.**

R. R., male, aet. 34 years, an ex-soldier, was admitted to the Edinburgh Royal Infirmary complaining of headache and dimness of vision.

**History.** Two years previously he had suffered from severe nocturnal headaches, and he lost the power of his left arm and leg. In the course of two months the left hemiplegia was recovered from under
anti-syphilitic treatment. Five days prior to admission he began to suffer from severe headache, his sight rapidly became dim, and he lost the power of his left arm.

Condition on admission. On admission he was in a dazed, stupid condition, complaining of intense occipital headache. Visual acuity was much diminished and the fields of vision were restricted, but no accurate observations could be made owing to his mental condition. The left arm was completely paralysed, but there was no evidence of weakness in the left leg, and the reflexes in that limb were normal. On admission the cerebro-spinal fluid was examined and found to contain 110 lymphocytes per field. A syphilitic lesion of the brain was accordingly diagnosed, and energetic antisyphilitic treatment was adopted, but without avail. He rapidly became worse, his sight failed utterly, and he passed into a condition of coma which terminated in death five days after admission. Shortly before
death a quantity of cerebro-spinal fluid was withdrawn in the hope of relieving the increased intra-cranial pressure which seemed to be present. To my surprise I found that the fluid was turbid (the turbidity not being due to blood), whereas on the previous occasion it was quite clear. On being centrifuged for half-a-minute a thick layer of pus formed at the bottom of the tube, and the resulting film was so thick that the cells were uncountable. A thin film was then made, and the differential count showed that there were 57 polymorphs to 47 lymphocytes.

At the autopsy the remains of an old granulomatous lesion were found at the posterior end of the first right frontal convolution. This, then, was the cause of the hemiplegia two years previously; it was also the cause of the lymphocytosis which proved to be grievously misleading. For two acute abscesses were present, one in the right motor area, the other in the centre of the left occipital lobe. The pus from this latter abscess had made its
way into the lateral ventricles, and thence to the base of the brain through the locus perforatus posticus. This, of course, was the cause of the polymorphonuclear leucocytosis in the cerebro-spinal fluid. 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, although in the present instance the information thus acquired was unable to save the patient's life. I know of no better example of this than is afforded by the present case, unless it be the case of intra-cranial haemorrhage, in which the presence of blood in the cerebro-spinal fluid gave Guthrie an indication which caused him to try phine, tie the ruptured artery, and thus save the patient's life. The case just described is fully reported in Byrom Bramwell's "Clinical Studies", where photographs are given showing the two abscesses and the old gumma.

Case II. Tumour of the Pituitary Body. W. J., male,
act. 36 years, was admitted to the Derby Borough Asylum in December 1909.

**History.** For the last eight years he had suffered severe neuralgic pains in both temples. Six and a half years ago the sight in the left eye began to fail, and six months later the right eye followed suit. He was treated in several hospitals with large doses of iodide of potash, but both the sight and the headaches became steadily worse. In June 1905, he began to take epileptic fits and continued to do so; they presented no localising symptoms. Finally he became acutely maniacal and had to be removed to the asylum. It should be mentioned that there was no history or evidence of syphilis.

Condition on admission. Patient was a stout man, and was said to have become considerably stouter during the last two years. He was in a dazed, stupid condition, with no control of his vesical and rectal sphincters. There was no polyuria, and his urine contained neither albumen nor sugar. From his left nostril there
was a discharge of clear, serous fluid, which appeared when he sat up in bed, and which fell drop by drop. It was highly albuminious, and on centrifuging was found to contain numerous leucocytes—both polymorphs and lymphocytes. As regards his nervous system, no paralysis of the arms or legs could be detected, nor any definite disturbance of sensation. He was very ataxic, even when sitting up in bed. The superficial reflexes were normal, but the deep reflexes were considerably exaggerated, those in the left leg being the most active. The plantar reflex was flexion. There was weakness of all the extrinsic muscles of the left eye, the weakness being most marked in the superior rectus, internal rectus, and inferior oblique. The pupils were medium, equal, regular, but reaction to light was sluggish in the right eye and completely lost in the left. There was complete amblyopia, and double primary optic atrophy. The fields of vision were taken in 1903, when it was found that the left eye was only
Fields of vision from the case of Pituitary Tumour, showing temporal hemianopia on the right side, and great restriction of the field on the left.
capable of perceiving hand movements, while the right field of vision presented a perfect example of hemianopia, the temporal half of the field being quite blind. The charts are given on page 87. The condition of the cerebro-spinal fluid was remarkable. It came out under markedly increased pressure, was quite clear, and contained an enormous quantity of protein. The Kuguchi reaction was very marked, and the ammonium sulphate test was positive with a dilution of 1 in 15. But the most extraordinary feature was the cell-count which gave an average of 1630 per field, almost all the cells being lymphocytes.

The patient remained in a dull, stupid and confused condition, passing the greater part of the day in sleep, from which it was difficult to arouse him, and taking occasional epileptic fits in which no sign of localising value was observed. He died with startling suddenness four months later.

Post-mortem examination. No signs of disease
Photograph of floor of skull from the case of Pituitary Tumour, showing the erosion produced, and the slit-like openings into the Antrum of Highmore on either side which were the cause of the cerebro-spinal rhinorrhoea.
in the thoracic or abdominal organs. At the base of the brain there was a large, soft, friable, vascular tumour of a fleshy colour, which was growing downwards into the sella turcica, from which cavity it had to be torn before the brain could be removed. A mass of pulpy vascular material, not unlike red currant jelly, was left in the pituitary fossa. The tumour was then seen to be growing from the infundibulum, this being the only point at which it could not be separated from the brain. In consistency it was gelatinous, and in places almost cystic. Its length was 7.2 cm, its width 5.3 cm, and it extended from the optic chiasma to the middle of the pons. The most striking changes, however, were those in the floor of the skull. The sella turcica had developed into a huge cavern 6.5 cm long and 4 cm wide. Opening out of it on either side was an oval aperture, well shown in the accompanying photograph, that on the left side proving on investigation to communicate with the antrum of Highmore. Thus the
Section of the Pituitary Tumour which was associated with a very marked cerebro-spinal lymphocytosis and increase in the protein content.

The same more highly magnified, showing the large blood-spaces which characterised the tumour.
discharge from the left nostril, observed during life, was in reality a discharge of cerebro-spinal fluid from the cranial cavity. Microscopic examination of the tumour showed it to consist chiefly of large round and oval cells containing a large and distinct nucleus; there were numerous large thin-walled blood spaces, and here and there fibrous trabeculae running through the tissue; the whole bore a close resemblance to a mixed-cell sarcoma. Some idea as to the microscopic appearance of the tumour may be gained from the micro-photographs on page 91, but it may be mentioned that the slides were much superior to the photographs. A full description of this case was published in the "Lancet" (67).

The lesson which this case teaches us is that a great increase in the protein content and an enormous lymphocytosis are not necessarily due to a syphilitic or para-syphilitic lesion. It is possible, that the fact of the tumour being one of the pituitary-body may have had some bearing on the anomalous condition of
the cerebro-spinal fluid, but I have been unable to find in the literature of pituitary tumours any reference to the cerebro-spinal fluid. It is to be hoped that in future descriptions of these cases such reference will be made.

Case III. General Paralysis. I do not propose to describe this case in detail for it was a simple straightforward case of general paralysis in a man aged thirty. There was a definite history of syphilis. Both the motor and the mental symptoms were typical of general paralysis in an early stage. The case was fully described in the "British Medical Journal." (68)

It is to the cerebro-spinal fluid that I wish to draw attention. The fluid came out under distinct pressure; it was very slightly turbid; this turbidity was not due to the admixture of blood; it was alkaline in reaction. The film presented an extraordinary appearance. Here and there the leucocytes were collected in great masses several layers thick, being more
sparingly distributed between the masses. In places where the distribution was fairly uniform there were about 3,400 cells to the field. The differential count showed that polymorphs were present in the proportion of 1 to 5; the lymphocytes varied considerably in size, the great majority being small. A very large amount of protein was present, but a quantitative estimation was not made. The fluid was examined as many as seven times, and on each occasion this enormous leucocytosis was present. I detail this case because so far as I have been able to ascertain, this leucocytosis easily holds the record.

Case IV General Paralysis. This case was also a typical one of general paralysis, so that a detailed description is not necessary. The patient was lumbar punctured on September 27th, 1910, soon after admission, being at that time in a restless, excited condition. The fluid that was first withdrawn was very turbid, this turbidity being due to the admixture of blood. I made several
other punctures at different levels on this occasion, supposing that the blood came from an injured vessel, but each time with the same result. I then centrifuged the fluid for some hours; a thick deposit of blood collected at the bottom of the tube, but the supernatent fluid remained of a canary yellow colour. Now, when blood is added to the fluid and the mixture centrifuged, the supernatent fluid ought to be perfectly clear and colourless, whereas if the blood is due to a cerebral or spinal haemorrhage the supernatent fluid remains tinged, owing doubtless to the haemoglobin being dissolved out. The fluid was again withdrawn on September 11th, this time it was quite clear but distinctly yellow. On September 21 it was very faintly tinged. On October 17 there was again blood, but it had obviously come from the subarachnoid venous plexus, and the fluid became perfectly clear and colourless on being centrifuged. On November 28 the fluid was clear and colourless. A marked lymphocytosis
was present on each occasion, but the Koguchi reaction was never marked, and was doubtful at times, and the ammonium sulphate test gave a ring only once with a dilution of 1 in 4, every other time only giving it with a dilution of 1 in 2.

The question is: was the blood present on the first occasion derived from an outside source, or was it due to previous haemorrhage into the fluid? If the latter explanation be the correct one, what was the nature and the cause of this haemorrhage?

Case V. Epileptic insanity. J. H., male, aet. 53 years, was admitted to the Derby Borough Asylum in September 1910, in a restless, excited condition, with marked delusions of a religious nature. Three years previously he sustained an injury to the head, and since then has had three or four fits of an epileptiform nature. He soon settled down and lost his delusions, although he remained of a very religious turn of mind. The cerebro-spinal fluid was examined soon after admission, and the results were
as follows:—cell-count 6, Houghchi negative, a doubtful ammonium sulphate reaction given with the undiluted fluid. All the cells were small lymphocytes.

On March 10th, 1911, he took a severe epileptic fit, and became very restless, noisy and excited, wanting to fight all those about him, and shouted, sang, and prayed for three days on end. He had the most vivid auditory and visual hallucinations, all of a religious nature, and carried on long conversations with the Almighty.

His cerebro-spinal fluid was examined on March 13th, and it was found that he had a lymphocytosis of 59; of these, 68 per cent. were small lymphocytes and 32 per cent. were large lymphocytes. What the meaning of this increase in the number of large mononuclears is I am unable to say. The fluid was examined on March 14th, 15th, 16th, and 17th, and the lymphocytosis, together with the differential count, is given in Table X. On one or two occasions a few polymorphs were noticed. It will be seen that the cell-count varied from
day to day, being highest at the last examination. In every case except one, however, the increase was marked. The Kuguchi and ammonium sulphate tests were negative. This is the only case I have encountered, with the exception of the case of cerebral gumma and abscess just described, in which a marked change in the cerebro-spinal fluid occurred during the course of the illness.

Discussion of Results.

What, then, is the meaning of the facts which emerge from the series of observations described in these pages? It is evident that in certain pathological conditions (for we cannot conceive that any of these conditions are physiological), the cells in the cerebro-spinal fluid, for some reason or other, become increased in number. What is the reason and meaning of this increase? Before this question can be answered, the source of these cells must
be determined. There can be little doubt that in the pia mater we have the origin of most of the cells. That they are not derived from the blood is evident from the fact that polymorphs are never found in the fluid during health. It is true that Rokitansky doubted whether the cells could come from the pia, because in cases of general paralysis he found mast cells in the pia, but none in the fluid. Alzheimer, however, by using an improved technique, succeeded in demonstrating the presence of mast cells in the fluid. In the pia of cases which come to autopsy are found approximately the same kind and number of cells which appear in the corresponding fluids; in general paralysis the perivascular lymphatics of the pia are densely infiltrated with lymphocytes, whilst a corresponding increase is found in the fluid. It may be taken as proved, therefore, that the pia mater is the origin of these cells. That being so, it is almost certain that a cell increase is due to some form of irritation of the leptomeninges, although Mez Bacher of Heidelberg denies
this doctrine very strenuously.

The occurrence in the nervous fluids of a definite increase in the cerebro-spinal cell-count is a well recognised fact. It is almost certainly due to the syphilitic toxin irritating the meninges, and causing them to produce an abnormal number of cells. The leucocytosis which is so constantly present in tuberculous meningitis is due to a similar cause. The question now arises: what is the cause of the cellular increase in those cases where neither the syphilitic nor the tubercular factor is at work? That an increased cell-count cannot in all cases be regarded as toxic in origin seems to be indicated by the two examples of congenital imbecility which presented a moderate lymphocytosis. It must be remembered, however, that all the other cases of imbecility showed no abnormality, and it is possible that in these two cases a toxic element was present, for a congenitally weak nervous system would be more susceptible to toxic invasion than a sound one.
Again, why should some epileptics have an increased cell-count and not others? The cause of epilepsy is still one of the unsolved problems of mental science, but the modern view is that to a congenitally weak nervous system is added some factor producing special stress — it may be merely the strain placed on the developing organism at the time of puberty, or it may take the form of some toxic irritant. If this be so, then the cases which present a lymphocytosis may be those in which some toxin (at present unknown) plays an etiological part. It will be recalled that in one case of epilepsy the cell-count became greatly increased after a fit, the patient not having had a fit for several months. The lymphocytosis was not caused by the fit, but was due to the same cause as produced the fit — in all probability some form of toxæmia. It is not necessary that the irritant be bacterial in nature in order that a proliferation of cells may be induced. This has been shown experimentally by Burves Stewart (74), who succeeded
Inciting an abundant leucocytosis in monkeys by injecting sterile salt solution into the spinal theca. There is little doubt that a toxic factor was present in the ten cases classed as dementia praecox. The fact that blood examination revealed no evidence of a toxæmia counts for nothing, because it is only to the acute infections that the blood cells respond, whereas they show no change in the chronic infections such as tubercle and syphilis. I have pointed out that in all of these cases there was the probability of the congenital element being present, but this in no way excludes the possibility of a toxæmia; indeed, it is probable that it predisposes to and prepares the way for such a toxæmia, just as the syphilitic virus prepares the way for the actual exciting cause of general paralysis, whatever that may be.

There can be no doubt that many other nervous and mental conditions are toxic in origin, although our coarse methods
of examination have failed to reveal the presence of a toxin. Such a disease, for example, as disseminated sclerosis bears the closest resemblance to a toxic condition: the suddenness with which the symptoms may appear, the remarkable way in which they may clear up for a time, the diffuseness of the pathological findings, and the selective action on certain parts of the neuromuscular element, all point clearly to the action of some toxin, and that evidence of the presence of this toxin in the cerebro-spinal fluid will be found some day is, I think, certain. An even more typically toxic condition is acute anterior poliomyelitis. It is of the greatest interest, therefore, to learn that Flexner and Clark (73) of the Rockefeller Institute have quite recently described a marked increase both in the cells and the protein content in this condition; the cells are partly of the polymorphonuclear and partly of the mononuclear type, and the protein is detected by Hiyouchi's butyric acid test.
What the significance of an increase of protein content may be it is still more difficult to say. The protein must be derived from the blood, and apparently in certain conditions the permeability of the walls of the capillaries becomes increased. The syphilitic virus is certainly the most important in the production of this condition, and the largest amounts are met with in tabes dorsalis and general paralysis, but whether a protein increase is always to be regarded as indicative of a toxæmia, and what its significance may be in such conditions as pituitary tumour, epilepsy, acute mania, alcoholic excitement, dementia praecox, and congenital imbecility, we are not at present in a condition to say.

I do not consider that the results obtained in the examination of the Fehling-reducing power of the fluid are definite enough to enable me to discuss them adequately, but I regard it as highly probable that further investigations on this subject may
in the future yield information of the greatest importance.

Conclusions.

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

2. There is a remarkable diversity of opinion on some of the most important points in connection with the cerebro-spinal fluid. I have endeavoured as far as possible to reconcile these conflicting statements, but there are certain points on which my own results are strongly opposed to those of some former observers.

3. A study of the fluid from the same
case on a number of different occasions has shown that Widal's method of cell enumeration is satisfactory for comparative purposes.

4. Repeated examinations of the fluid from the same case may yield valuable indication as to cerebral and meningeal changes which are taking place.

5. The butyric acid reaction of Noguchi is characteristic of general paralysis and tabic 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 of determining the dilution of cerebrospinal 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. The relationship between cell-count and protein content is close, but not invariably constant.
With regard to general paralysis and tabes dorsalis the views of other observers have been fully corroborated. An increase in the number of lymphocytes and in the protein content is the almost invariable rule.

This increase is by no means confined to these conditions and to tubercular meningitis, as has been commonly supposed. It has been shown that such an increase may occur in a variety of other conditions.

A definite group of cases, bearing a strong family likeness to one another, and approximating more closely to dementia praecox than to any other recognised form of insanity, has been isolated; these cases presented a lymphocytosis which was always distinct, and occasionally very marked.

The cytological changes in the cerebro-spinal fluid in the ordinary insanities are not accompanied by corresponding changes in the blood.

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

14. 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 24 hours.

15. These unpleasant results are not accompanied by appreciable alterations in the blood-pressure.

16. I shall conclude by quoting some remarks of Ernesto Lugaresi (75) on the examination of the cerebro-spinal fluid: "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."

(Signed) William Boyd.
Table I showing the extent to which the Cell Count varied in the same case.

<table>
<thead>
<tr>
<th>No.</th>
<th>Condition</th>
<th>Cell Count on different occasions</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>Acute mania</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>do</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>do</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>do</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>do</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>Chronic mania</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>Paranoia</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>Congenital imbecility</td>
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</tr>
<tr>
<td>9</td>
<td>Melancholia</td>
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<tr>
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<td>12</td>
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<td>13</td>
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</tr>
<tr>
<td>14</td>
<td>do</td>
<td>26</td>
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<td>15</td>
<td>Epileptic insanity</td>
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<td>16</td>
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<td>General paralysis</td>
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<td>21</td>
<td>Tabes dorsalis</td>
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<tr>
<td>Condition</td>
<td>No. of cases</td>
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<td></td>
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<td>Sibes dorsalis</td>
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<tr>
<td>General paralysis</td>
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<td>Disseminated sclerosis</td>
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<td>13</td>
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<td>10</td>
</tr>
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<td>Dementia praecox</td>
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<td>1</td>
</tr>
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<td>Jobe circulaire (excited stage)</td>
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<td>1</td>
</tr>
<tr>
<td>Alcoholic excitement</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Congenital imbecility</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Secondary dementia</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Acute suppurative meningitis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Congenital syphilis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Aortic aneurism</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Aortic incompetence</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>117</strong></td>
<td><strong>71</strong></td>
</tr>
<tr>
<td>No.</td>
<td>Condition</td>
<td>No of cases</td>
</tr>
<tr>
<td>-----</td>
<td>----------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>1</td>
<td>Acute mania</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>do do</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>do do</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>do do</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>Chronic mania</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>do do</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>Dementia praecox</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>do do</td>
<td>2</td>
</tr>
<tr>
<td>16</td>
<td>do do</td>
<td>2</td>
</tr>
<tr>
<td>18</td>
<td>do do</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>do do</td>
<td>3</td>
</tr>
<tr>
<td>22</td>
<td>General paralysis</td>
<td>2</td>
</tr>
<tr>
<td>24</td>
<td>Secondary dementia</td>
<td>2</td>
</tr>
</tbody>
</table>
Table IV showing the Protein Content expressed in terms of the dilution of Cerebro-spinal Fluid which gave a positive reaction with the Ammonium Sulphate test.

<table>
<thead>
<tr>
<th>Condition</th>
<th>No of cases</th>
<th>Negative result</th>
<th>Diluted fluid 1 in 2</th>
<th>1 in 4 to 6</th>
<th>1 in 7</th>
<th>1 in 10 to 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tabes dorsalis</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Tabo-paresis</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>General paralysis</td>
<td>5</td>
<td></td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pituitary tumour</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Acute mania</td>
<td>12</td>
<td>5</td>
<td>6</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic mania</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melancholia</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>14</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary dementia</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia praecox</td>
<td>10</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confusional insanity</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stuporose insanity</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paranoia</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folie circulaire (excited stage)</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholic excitement</td>
<td>2</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital imbecility</td>
<td>14</td>
<td>10</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital syphilis</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic rheumatism</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>86</strong></td>
<td><strong>41</strong></td>
<td><strong>26</strong></td>
<td><strong>8</strong></td>
<td><strong>4</strong></td>
<td><strong>3</strong></td>
</tr>
</tbody>
</table>
Table V showing results of the Noguchi test.

<table>
<thead>
<tr>
<th>Condition</th>
<th>No of cases</th>
<th>Positive</th>
<th>Doubtful</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaimes</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Jaibo-paresis</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>General paralysis</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pituitary tumour</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dementia praecox</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>15</td>
<td>2</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Melancholia</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Other conditions</td>
<td>54</td>
<td>0</td>
<td>0</td>
<td>54</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100</strong></td>
<td><strong>15</strong></td>
<td><strong>4</strong></td>
<td><strong>81</strong></td>
</tr>
</tbody>
</table>
Table VI showing a series of 17 cases in which an increase in the Cell Count was not accompanied by a corresponding increase in the Protein Content.

<table>
<thead>
<tr>
<th>No.</th>
<th>Condition</th>
<th>Cell Count</th>
<th>Noguchi Pos.</th>
<th>Noguchi Neg.</th>
<th>Ammonium Sulphate test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chronic mania</td>
<td>14</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Epilepsy</td>
<td>80</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>do</td>
<td>84</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>do</td>
<td>54</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>do</td>
<td>29</td>
<td>?</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Dementia praecox</td>
<td>121</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>do</td>
<td>15</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>do</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>do</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>do</td>
<td>26</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>do</td>
<td>33</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>do</td>
<td>41</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>do</td>
<td>70</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>do</td>
<td>19</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Congenital imbecility</td>
<td>25</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>do</td>
<td>18</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Alcoholic excitement</td>
<td>12</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Severe headache coming on 48 hours after getting up.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ditto</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Headache and nausea coming on 3 days after.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Vomited</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Ditto</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>For several days sick whenever he got up.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Vomited</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Headache. On a second occasion kept in bed 48 hours - no headache.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>For several days sick and faint each time on getting up.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Sick for several days.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Vomiting which brought on an exacerbation of gastric ulcer.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Headache and sickness on getting up after being 48 hours in bed.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Headache and nausea.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Pallor, nausea, off food for a week.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Headache on getting up after being 48 hours in bed.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Sick and upset for a week.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Severe headache, but refused to stay in bed.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Vomited 3 days later, although in bed all the time.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Vomited 8 hours after getting up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Headache and vomiting on 2 occasions.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Headache, vomiting and collapsed.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Vomited 2 days later although still in bed.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>On getting up on the 5th day headache and faintness came on 7 hours later.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table VIII showing variations in Blood Pressure (expressed in terms of millimetres of mercury) due to Lumbar Puncture.

<table>
<thead>
<tr>
<th>No.</th>
<th>Condition</th>
<th>Blood Pressure Before puncture</th>
<th>Blood Pressure After puncture</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>General paralysis</td>
<td>130</td>
<td>126</td>
</tr>
<tr>
<td>2</td>
<td>Dementia praecox</td>
<td>130</td>
<td>124</td>
</tr>
<tr>
<td>3</td>
<td>Epileptic insanity</td>
<td>106</td>
<td>108</td>
</tr>
<tr>
<td>4</td>
<td>do</td>
<td>120</td>
<td>108</td>
</tr>
<tr>
<td>5</td>
<td>do</td>
<td>106</td>
<td>112</td>
</tr>
<tr>
<td>6</td>
<td>do</td>
<td>120</td>
<td>118</td>
</tr>
<tr>
<td>7</td>
<td>do</td>
<td>118</td>
<td>112</td>
</tr>
</tbody>
</table>
Table IX showing the Relation between the Cells of the Blood and of the Cerebro-spinal Fluid.

<table>
<thead>
<tr>
<th>Cerebro-spinal No.</th>
<th>Lymphocytes</th>
<th>Total Leucocytes</th>
<th>Polymorphs</th>
<th>Small lymphs</th>
<th>Large lymphs</th>
<th>Eosinophils</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>10,000</td>
<td>60%</td>
<td>30%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>2</td>
<td>121</td>
<td>9,600</td>
<td>75%</td>
<td>14%</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>9,600</td>
<td>62%</td>
<td>28%</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>9,400</td>
<td>76%</td>
<td>14%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>7,600</td>
<td>77%</td>
<td>15%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>10,200</td>
<td>78%</td>
<td>14%</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>10,100</td>
<td>62%</td>
<td>22%</td>
<td>13%</td>
<td>3%</td>
</tr>
<tr>
<td>8</td>
<td>33</td>
<td>8,200</td>
<td>75%</td>
<td>16%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>9</td>
<td>41</td>
<td>10,000</td>
<td>67%</td>
<td>19%</td>
<td>13%</td>
<td>1%</td>
</tr>
<tr>
<td>10</td>
<td>70</td>
<td>9,000</td>
<td>73%</td>
<td>20%</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>
Table X showing the marked change in the cerebro-spinal cytology of the case of Epileptic Insanity described in the text.

<table>
<thead>
<tr>
<th>Date</th>
<th>Total Cell Count</th>
<th>Differential Cell Count</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Small lymphos</td>
</tr>
<tr>
<td>Sept 26th 1910</td>
<td>6</td>
<td>100%</td>
</tr>
<tr>
<td>March 13th 1911</td>
<td>39</td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>75%</td>
</tr>
</tbody>
</table>
References

(1) J.W. Mott  "Oliver Sharpey Lectures 1910"
     Lancet, July 2nd and 9th, 1910

(2) J. Scott Williamson  "The cerebro-spinal fluid in general paralysis and the nervous lues"

(3) Mott  loc. cit.

(4) Winifred Muirhead  "The Wassermann reaction in the blood and cerebro-spinal fluid, and the examination of the cerebro-spinal fluid in general paralysis and other forms of insanity"

(5) Nicol  Centralbl. f. Nervenheilk. u. Psychiatri. April, 1904


(7) Tissot  Le Prog. Med. May 15, 1908

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