The results of work published by various workers have been quoted to indicate that positive results depend on disordered functioning of the vegetative nervous system. Investigation at the Maudsley Hospital has tended to confirm this. The results of this much larger investigation will probably be published shortly, but the results obtained in this series of cases would indicate that there is, in the psychoses, a tendency to disturbance of the vegetative nervous system, and that the disturbance holds some relation to the severity of the symptoms.

I desire to express my thanks to Dr. Golla, at whose suggestion this research was carried out, and whose advice and guidance have rendered it possible. My thanks are due also to the Superintendents of Colney Hatch, Long Grove, and Banstead Mental Hospitals for permission to carry out these tests.

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Some Notes on Encephalitis Lethargica.[1]

By Robert Marshall, M.D., F.R.C.P.I., D.P.H., Belfast.

The following notes are derived from the case-records of the Royal Victoria Hospital, Belfast, by kind permission of the medical staff, and are placed before you on the suggestion of Col. Dawson. They are an analysis of a series of 42 cases of encephalitis lethargica treated as in-patients of the Hospital between October 5, 1918, when the first case was admitted, and December 31, 1923. Of these 42 patients, 14 died in hospital, and of 28 who survived 2 died within a year of leaving hospital; 18 replied either in person or by letter to my circular letter of inquiry, and I was unable to trace the remainder.

The age, sex, year and seasonal distribution of these cases is stated in the table before you, from which it will be seen that the majority of cases occurred in the second decennium, but that no age-period is exempt. This corresponds closely to the English

[1] A paper read at the Annual Meeting held at Belfast, July 3, 1924.

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figures, published in the Report to the Ministry of Health in 1922, where 25 *per cent.* of cases occurred between 10 and 20 years.

The male sex suffered more severely than the female, there having been 30 male cases with 11 deaths as compared with 12 female cases with 3 deaths. This contrasts with the English figures, which show almost equal incidence on the sexes, but confirms Schulze's (1) figures of American cases, where the majority were males. There was 1 case in 1918, there were 2 in 1919, and in 1920 there arose a much more definite outbreak: 19 cases were admitted to the Royal Victoria Hospital, of whom 6 died. Three cases in 1921 and only 1 in 1922 showed a marked lull, followed by a rise to 16 cases in 1923, of whom 7 died in hospital.

These cases did not represent the whole incidence of the disease in the city during these years, as the deaths reported from this cause in the County Borough of Belfast (2) are as follows:

1918	3 deaths.
1919	7 ,,
1920	24 ,,
1921	5 ,,
1922	3 ,,
1923	20 ,,

Again I think it may be said that in many of these cases the diagnosis presented unusual difficulty, and for that very reason they were sent to the Royal Victoria Hospital for investigation.

The death-rate for the 42 cases was thus $33\frac{1}{3}$ *per cent.*, if we exclude the 2 patients who died some months after leaving hospital, and in whom I cannot be certain that the deaths were due to encephalitis.

The death-rate in the 1,723 cases investigated by McNalty, Parsons and Perdrau (3) was 48·3 *per cent.*; the French death-rate (4) in 1920 was $33\frac{1}{3}$ *per cent.* The American Commission (5) states that the deaths in the acute stage varied from 10 to 20 *per cent.* The present epidemic in Belfast has so far given rise to 211 cases with 17 deaths (June 21, 1924).

The seasonal incidence shows a contrast to that found in the English records; our worst months were April, May and June, and this is again noticeable in 1924; in England, certainly until 1922, the worst month was January.

I have not found any evidence of contagion amongst these cases, and in my circular letter to survivors, the question, "Has there been any other person in your family, or living in the same house, who has suffered from a similar attack to yours?" has always been answered in the negative. This only proves, I fear, the inadvisability of forming a conclusion on the analysis of too short a

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series of cases; as the English report states—" If, in amount, the evidence concerning the contagiousness of encephalitis lethargica is small, it may be said that some of it at least is good." Netter (4), of Paris, found evidence of contagion in 4·6 *per cent.* of cases in the 176 which he personally investigated.

Symptomatology.

I am at a loss to give you any clear and succinct account of the clinical condition of these 42 patients. As Achard (2) says, " The clinical diversity is such that not only can two patients present no apparent resemblance, but more, in the same patient, at different phases of the malady, one would be inclined to believe in several successive illnesses."

To classification of types of encephalitis there is no end. Cruchet (7), for example, recognizes nine types. The American Commission (5) recognized ten. Walshe (8) in 1921 deplored the multiplication of such classifications, and suggested analysis of the symptoms on the following schema:

- General (toxi infection)
  - Fever.
  - Shivering.
  - Eruptions.
  - Pains and malaise.
  - Gastro-intestinal disorders.
- Nervous
  - General
    - Positive
      - Delirium.
      - Mania.
      - Restlessness.
      - Hallucinations.
    - Negative
      - Lethargy.
      - Coma.
  - Localizing
    - Positive
      - Convulsions.
      - Involuntary movements.
      - Muscular contractions.
      - Rigidity ataxy.
      - Pain.
    - Negative
      - Paralyses.

In Walshe's own words: " The terms positive and negative are employed in the sense in which Hughlings Jackson originally used them; positive symptoms being the expression of exalted function either from irritation or from loss of higher control, and negative symptoms expressing loss or depression of function from destruction of nervous structures or otherwise."

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I have accordingly attempted to work on such a plan and have embodied my results in a tabular statement.

The diagram shows the comparative incidence of the principal symptoms as recorded in the Royal Hospital series of 42 cases as compared with the Ministry of Health series of 1,264. It is, I think, rather remarkable that for the most part the figures should be so alike, the figures for complete coma, and the death-rate in comatose cases and those for delirium being particularly striking.

It is noteworthy, I think, that the average highest recorded temperature among the surviving cases was 99·2°, whereas the average highest recorded temperature among the fatal cases was 102·7°. Of these 14, 13 died during a rise of temperature, in several cases amounting to a definite hyperpyrexia. This terminal hyperpyrexia is a frequent feature of encephalitis lethargica, and has been described (9), but has not perhaps been sufficiently emphasized Hume and Shaw (10), in their analysis of 20 cases in 1922, note that 3 of the 4 fatal cases died in hyperpyrexia. I think that if one's encephalitic patient shows a definite tendency to a secondary rise of temperature the prognosis is decidedly changed for the worse. There was no case of "inverted" temperature in the series. Skin eruptions were more common than I had suspected—a transient erythema was the most usual. Profuse sweating could not always be accounted for by any therapeutic effort, such as aspirin or salicylic acid. I take it that the severe pains so commonly complained of are due to the peripheral nerve and root involvements which have been the subject of inquiry by Kennedy and Abrahamson. (5)

Insomnia occurred in 42 *per cent.* of the fatal cases as compared with 14 *per cent.* of the survivors, and was in 4 cases on onset phenomenal. One seems to have seen many more of these cases of what might be called a hyposomnic onset in the 1924 epidemic than formerly; this may be due to earlier recognition of symptoms by the patient himself, or possibly to the variation which is said to occur between one epidemic and another.

Lethargy, not deepening to coma, occurred in 54·7 *per cent.* of cases, and actual coma in 23·8 *per cent.*

Involuntary movements present one of the most difficult problems in this disease, as they may vary from time to time in the same patient. The choreiform type is recorded in 11·9 *per cent.* of cases and some form of muscular twitching in 45 *per cent.* These figures do not present any marked difference from the English figures, and this also applies to the proportion of cases in which rigidity was noted (2·3 *per cent.*). A glance at the diagram shows that the foregoing symptoms and signs occurred with extraordinary similarity in the large series (1,264 cases) as compared with the

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small series at present under review. This is not the case in the last lines of the diagram, and I can offer no explanation of why paralysis of one or more limbs was noted in 9·5 *per cent.* of the Royal Hospital series as compared with 61 *per cent.* in the larger group.

I have constructed a similar table to place quickly before you the comparative incidence of the ophthalmological signs; and for comparison I have included the results of the series of 1,152 cases recorded in the Ministry of Health monograph, and in 100 cases personally investigated by Dr. Ward A. Holden at the Mt. Sinai Hospital. Ptosis was apparently not so frequently noticeable in the Royal Victoria Hospital cases, but on the other hand diplopia was recorded in 45 *per cent.*; strabismus in 11·9 *per cent.* and nystagmus in 9·5 *per cent.* Of 234 cases analysed in the English Report, 5·5 *per cent.* showed true optic neuritis and 19 *per cent.* showed signs portending the same. Optic neuritis occurred in 11·9 *per cent.* cases in the Royal Victoria Hospital series, and the observation has this value that it was made or confirmed in each case by an ophthalmological specialist.

As in the English series, these figures were thought to be high and the case-notes were carefully considered, but in each case the diagnosis of encephalitis was made on ample clinical grounds. There is no record of any case showing optic atrophy. Loss of the light reflex, loss of accommodation reflex, and loss of both, are each recorded in 7 *per cent.* of the cases.

It will thus be seen that fever, headache, lethargy, involuntary movements and diplopia are the most frequently noted symptoms, and I share the opinion expressed by Hall (11) and others that marked "general" signs are of worse import than marked "localizing" ones.

Cerebrospinal Fluid.

The cerebrospinal fluid was examined in 12 non-fatal cases and in 8 fatal cases. The cell-count varied from 0 to a maximum of 36 (in a fatal case diagnostically confirmed by autopsy). There were no constant changes to Lange's test. The most constant feature was the increased sugar content; in the earlier cases the test was not made quantitatively, but this was done in the later cases. In the fatal cases the highest figure was 0·13 *per cent.* and the lowest 0·076 *per cent.*, with an average of 0·108 *per cent.*; in the non-fatal cases the highest figure was 0·11 *per cent.* and the lowest 0·07 *per cent.*, with an average of 0·086 *per cent.* Thus the average sugar content was higher in the fatal than in the non-fatal cases.

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Dr. John A. Smyth, of the Bio-Chemistry Department, has supplied me with a longer series of figures, based on 42 cerebrospinal fluids examined by him between January, 1923, and June, 1924, the cases having been clinically diagnosed encephalitis lethargica in various hospitals or private practice.

The highest sugar content was 0·18 *per cent.*, the lowest 0·067 *per cent.*, the average 0·082 *per cent.*, and only 3 of the series were below 0·075 *per cent.* Achard explains the diminished sugar content of meningitis as due to the activity of the microbes inflaming the meninges, and argues conversely that in encephalitis there is a virus with greater affinity for the nervous tissues than for their coverings—a disease process in which microbic action is very slight or absent.

Whether this is a complete explanation is doubtful, but at least a raised sugar content appears to be of considerable diagnostic significance.

Post-mortem Results.

In 6 of the 14 cases which terminated fatally permission was obtained from the relatives that a *post-mortem* examination should be made. The results may be briefly tabulated thus:

Case D. 7: "Surfaces of both hemispheres showed small punctate hæmorrhages . . . choroid plexus markedly congested."

Case D. 6: "Acute congestion of surface of brain . . . congestion of vessels, most marked over occipital lobes . . . medulla and pons mottled with small punctiform hæmorrhages."

Case D. 5: "Punctate hæmorrhages of dura mater mainly in region of Sylvian fissure; marked reddening of pituitary. Petechial hæmorrhages of heart and diaphragmatic surface of right lung."

Case D. 4: "Small punctate hæmorrhages of medulla and pons . . . hæmorrhagic areas stomach and base of left lung."

Case D. 8: "Puncta cruenta in white matter of both hemispheres particularly well marked . . . pituitary surface normal, but markedly redder on section."

Case D. 9: "Petechial hæmorrhages in cerebrum, cerebellum and pituitary body."

After-History of Survivors.

Of the 28 survivors 18 replied either by letter or in person to my *questionnaire*. Six of the 18 now show a definite Parkinsonian syndrome, and all without exception complain of impaired health; "general weakness" is almost an invariable complaint, and 4 of

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the 12 specifically mention recurrent violent headache. One complains still of drowsiness, another of sleeplessness; 1 of twitching of her face; 2 complain of pain and weakness in arm and legs respectively. Two complain of speech defect, and one of these is, to my mind, worthy of special mention. Case C. 6, a woman æt. 40, was admitted to hospital in April, 1923, with a provisional diagnosis of uræmia. Her history was of a sudden attack of unconsciousness; she showed Cheyne-Stokes' breathing and was comatose on admission. There was albuminuria and there were hæmorrhages at the left retina, but her blood-urea content was 29 mgrm. per 100 c.c. and her urea concentration 2·7. There was marked twitching of the left arm. Her C.S.F. sugar content was 0·09 *per cent.* She rapidly improved and left hospital four weeks later, and when she reported in December I could find no physical signs of disease: her discs and retinæ were normal, and there was no albuminuria. She complained of being less fit for household duties, and of attacks of inability to speak: "I know rightly what's going on, but I couldn't utter a word to save my life." These attacks last for 20–30 minutes, and may recur once in a month or once in three months; she states that she is mentally clear during the attack.

Of the 6 with Parkinsonian signs 3 are noteworthy:

1. Case B. 3: Has the slow gait, rigid tremulous hands and mask-like face of the disease, but to my surprise his brother who brought him to hospital informed me that he earns his living as proprietor of a billiards saloon with three tables, and is capable of making a 40 "break."

2. Case A. 9 was æt. 16 at the onset of his attack in 1920, and was readmitted a year later suffering from paresis of his right arm, difficulty of speech and a return of his lethargy. His doctor reports to me (June, 1924) that he was of normal mentality before his illness, but is now mentally "simple," and at the age of 20 can earn only a slender wage delivering papers for a newsagent, and has well-marked Parkinsonian signs.

3. Case A. 4, whose age was 14 at the onset of his illness, shows the mask-like face, but his tremor mainly, if not altogether, involves his left side, and is so marked as to render him incapable of any accurate movements.

Of the remaining 3 Parkinsonian cases, 2 are in the Union Infirmary and all are incapable of work.

There appears to be no definite relationship between the intensity of the attack and the risk of development of the Parkinsonian syndrome; some of these Parkinsonian patients appear to have had typical but on the whole no more severe attacks than some who have recovered to a much greater extent. This confirms the

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view expressed by Hall (11) and others. The interval between the acute illness and the development of the syndrome also varies: one youth left the Royal Victoria Hospital in May, 1923, and on admission to the Union Infirmary in December, 1923, stated that he had never been able to go out of doors himself "for fear he would walk into something"; and I have within the past month seen a patient who had an acute attack in May, 1920, and who for three years and nine months later developed a coarse tremor of the left arm, which is probably a late sequela.

Differential Diagnosis.

The diagnosis of encephalitis may, in the majority of cases, be made on the clinical picture which the patient presents, combined with his history, even before the result of analysis of the C.S.F. is available. Prof. Hall (11), in his recently published book, gives a list of twenty-one conditions for which it may be mistaken.

Two additional conditions are diabetic coma and localized tetanus.

Glycosuria is not an uncommon phenomenon in encephalitis, and of course the disease may occur in a diabetic subject.

A. B—, æt. 66, was admitted to the Royal Victoria Hospital in May of this year complaining of thirst and of increasing weakness for three weeks; he also complained of diplopia, and there was slight generalized muscular twitching. His speech was indistinct and his cerebration slow. His urine contained sugar, acetone and diacetic acid. His case was considered *not* to be one of incipient diabetic coma on the following grounds: He had no "air-hunger," his skin was moist, his pulse full and bounding; there was no diminution of globular tension. His blood-sugar was 0·40 *per cent.*; his C.S.F. sugar 0·26 *per cent.* The acetonuria cleared up in five days on 10 units of insulin per day, and he remained free from acidosis, but he died comatose on the ninth day. Unfortunately a *post-mortem* was negatived by the relatives.

J. F—, æt. 48, was admitted to the hospital in April of this year, suffering from intensely painful spasmodic contractions of his abdominal muscles, particularly on the right side; these contractions lasted about one second and recurred at varying intervals, usually about three seconds in duration. He had had a boil on the left buttock some fourteen days before admission, but this was healed. A provisional diagnosis of localized tetanus was made and energetic treatment with anti-tetanic serum was instituted. On physical examination little was detected except the abdominal condition. His right knee-jerk was brisker than his left, and sudden extension of the right leg caused painful spasms of the right thigh. There was some rigidity of his back. There was no trismus, and there

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were none of the ocular signs of lethargic encephalitis. His C.S.F. sugar content was 0·087 *per cent.* and otherwise normal—no tetanus bacilli, negative Wassermann and Dreyer, Lange, cells and globulin. His condition slowly improved, the spasms becoming less frequent and severe, but when he left hospital he still suffered from occasional slight attacks, and he is still unable to resume his duties as an asylum attendant.

The points in favour of a diagnosis of tetanus are: The peculiarly severe character of the spasms and the occurrence of a septic focus a fortnight before (staphylococci are said to have the property of lighting up latent tetanus).

On the other hand, the cerebrospinal fluid findings, the prevalence of epidemic encephalitis, the occurrence of the spasms in the abdominal muscles, leaving the site of the boil unaffected, the absence of trismus and the doubtful response to large doses of serum are in favour of a diagnosis of encephalitis lethargica in an atypical form.

	1918.	1919.	1920.	1921.	1922.	1923.
Total cases	1	2	19	3	1	16
Died in hospital		1	6			7
Died after leaving hospital					1	1
Replied to circular		1	8	1		7
Unable to be traced	1		5	2		1
Males		1	15	2		12
Females	1	1	4	1	1	4
Ages 0–10						1
10–20		1	**2** 2	2		4
20–30		**1**	**1** 6			1
30–40			**1** 2	1		**3** 1
40–50	1		**1** 2			**1** 2
50–60			**1** 1		1	**3**
60–70						
Season—January to March		1	1	1		8
April to June			17	2		4
July to September			1		1	4
October to December	1	1				

Fatal cases are indicated by black figures.
Average duration of illness in fatal cases, 25·3 days.
If one unusually prolonged case is excepted, 13·4 days.
Average period in hospital of fatal cases, 5·2 days.

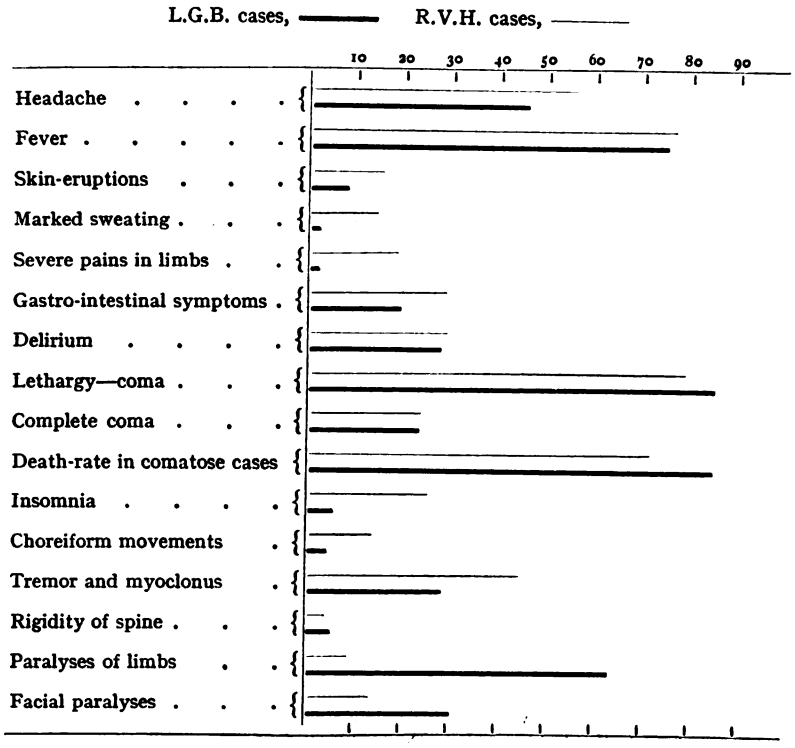
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The occurrence of such a case as this raises the question whether the cases described as localized tetanus in the past have not in some cases been manifestations of lethargic encephalitis. In his article on "Tetanus," published in 1916, Browning (12) quotes Evler as stating that amongst others the following are early symptoms of tetanus: Restlessness, changing to a desire to rest; sleeplessness and, it may be, nightly delirium; profuse sweating; darting pains in various parts; and, as later symptoms, nystagmus, strabismus, tremors and painless clonic spasms. All of these are, in the light of our recent experiences, highly suggestive of encephalitis lethargica.

Mental After-effects.

I do not feel qualified to deal with this aspect of the problem, but I could find no evidence of well-marked mental defect in any of the 18 cases I have traced, except in the case of the newsvendor's messenger already quoted.

Percentage of Cases in which Specified Symptom was recorded.



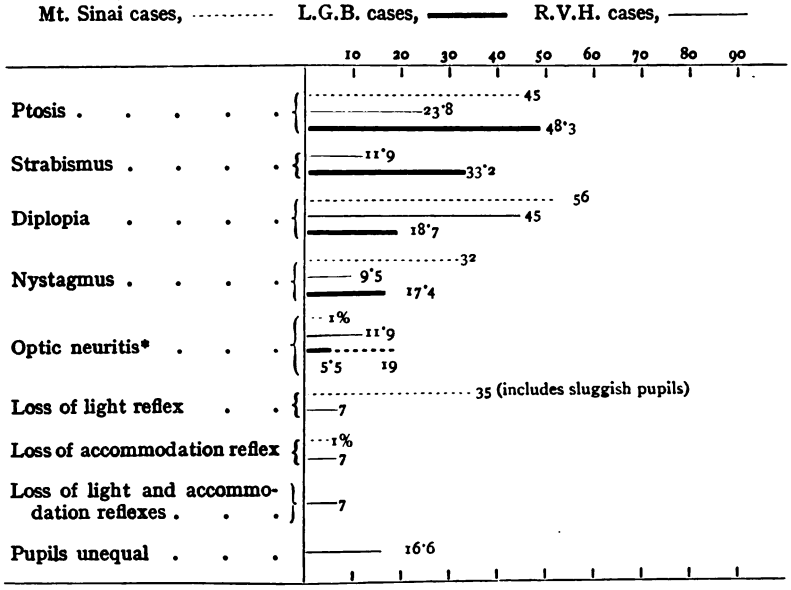
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I was interested to note in the report of Inspectors of Lunatics, Northern Ireland, for 1922 (13), that in no case had this disease been regarded as the cause of a patient's insanity. By Col. Dawson's permission I addressed a circular letter to the Medical Superintendent of each of the six asylums in Northern Ireland, but apparently there has so far been no admission to any of these institutions as a result of encephalitis, with the exception of one man with a very bad mental family history who was admitted to Downpatrick Asylum under the care of the President, suffering from acute encephalitis with marked mental symptoms. In England Prof. Hall reports that 30 mental cases of encephalitic origin have been admitted to asylums between 1918 and the end of 1922.

Apart from what one may term certifiable insanity, many of these patients are psychically the worse for their experience; they are for the most part depressed, as indeed their impaired health gives them reason to be. I have seen no case of euphoria as an after-effect.

The worst mental effect of the disease is undoubtedly on children, Wimmer (14) reports that 12 out of 25 children were mentally affected.

Percentage of Cases in which Specified Symptom was recorded.



* "In 5·5 *per cent.* of the cases in which the fundi were examined optic neuritis was present, while in 19 *per cent.* of these were present one or more signs portending the same."—*Ministry of Health Report*, p. 84.

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the most usual sequela being perversion of conduct. Inquiry amongst my colleagues leads me to believe that such cases are not unknown in Belfast, as in other cities. These patients present a problem both to their parents and to the State, and are potential recruits for the criminal lunatic asylums. I wonder how soon a past attack of encephalitis will be urged as a defence on a criminal charge!

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The Colloidal Gold Reaction with Cerebrospinal Fluid.

By THOMAS HOUSTON, *O.B.E.*, M.D., and EDWARD ARMSTRONG, M.B., from the Laboratory of the Royal Victoria Hospital, Belfast.

THE history of the colloidal gold reaction is one of great interest.

In 1901 Zsigmondy used the precipitation of colloidal gold by proteins as a means of determining quantitatively their amount in given solutions. He discovered that solutions of protein give protection to colloidal solutions of gold up to a certain point, and he determined the so-called goldzahl for various protein substances, by which is meant the number of milligrammes of protein employed, just sufficient to prevent the precipitation of 10 c.c. of colloidal gold of a percentage of ·0053 in the presence of 1 c.c. of 10 *per cent.* sodium chloride. By this method it can be determined whether a given protein is absolutely pure, or, granted that this is the case, how much of the protein is present in a given solution.

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