TUBERCULOUS MENINGITIS

with

Special Reference

to

Early Diagnosis

by

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I N D E X

PREFACE

The clinical material for the production of this thesis was obtained in the wards of Belvidere Fever Hospital, Glasgow and Heathfield Infectious Diseases Hospital, Ayr. I am indebted to Dr. Archibald for his kindness in granting me facilities for clinical, biochemical and bacteriological investigation in Belvidere Hospital and to Dr. Leask for similar facilities in Heathfield Hospital. Dr. Renolds, Pathologist to the Glasgow Corporation Hospitals, was of great assistance in demonstrating post mortem technique and in making helpful criticisms while the work was still in its early stages.

INTRODUCTION

Within the past three years a definite increase in the incidence of tuberculous meningitis has been observed. When this increase became obvious to me I was prompted to investigate the subject more extensively.

The investigation concerns itself with

1. The Etiology of the disease.
2. Pathology.
3. Clinical Signs and Symptoms.
4. A detailed examination of the Cerebro Spinal Fluid, which has as its main objective the early diagnosis of the disease.

1. The Etiology was studied with a view to discovering the main causative factors in this disease. This is of paramount importance in a disease like tuberculous meningitis which is practically always fatal because, if the causation is known for certain, steps can then be taken to diminish the incidence of the condition for which no known remedy has yet been found.

2. The Pathology of the condition was investigated primarily to verify the diagnosis arrived at by bacteriological and biochemical investigations and secondly to study the appearance of the brain in tuberculous meningitis and observe tuberculous lesions elsewhere in the body.

3. The Diagnosis of the disease at an early stage is most desirable. In view of the grave prognosis associated with tuberculous meningitis, it is a great advantage to the physician to be able to say at once, no matter how early in the disease, that this is or is not a case of tuberculous meningitis. If several days elapse before the relatives can be told that the condition is one of tuberculous meningitis and that the outlook is hopeless, they frequently express the opinion, although quite without foundation, that time has been wasted and that if a diagnosis had been made sooner something might have been done to save the patient's life.

With a view, therefore, to arriving at an early diagnosis, an investigation was made of the clinical signs and symptoms most commonly encountered in the early stages of the disease.

4. When tuberculous meningitis is suspected as a result of clinical observations an examination of the cerebro spinal fluid is the next step and this side of the problem was investigated in detail in order to demonstrate whether a definite diagnosis could be arrived at immediately from this examination.

The Etiology and Clinical Features are based on observations made on a series of 213 cases of tuberculous meningitis admitted to Belvidere Fever Hospital, Glasgow, during the period 1936 to 1940 inclusive.

The Pathological Observations are based on cases investigated by Dr. Renolds and myself at Stobhill Hospital, Glasgow, and Belvidere Hospital, Glasgow.

The Bacteriological and Biochemical investigations were made on a series of 42 cases seen during the years 1940 and 1941 at Belvidere Fever Hospital, Glasgow, and latterly at Heathfield Infectious Diseases Hospital, Ayr.

SECTION I.

ETIOLOGY.

In this section a review will be made of the age, sex and seasonal incidence of the disease, showing how it affects the younger age groups chiefly and how there is a tendency to greater incidence in the second quarter of the year.

Several factors have been stated to be important in the causation of tuberculous meningitis, and these will be investigated. It will be shown that measles whooping cough, and injury to the head are of minor importance in this respect and that the chief factor appears to be contact with a case of open pulmonary tuberculosis especially within the same household.

At present no remedy is available which will prevent the fatal termination of tuberculosis involving the meninges of the brain. In view of this unfortunate state of affairs it is of great importance that the onset of this condition should be prevented, if this is at all possible. In order to prevent the disease it is essential to have a thorough understanding of the etiological factors concerned and with this object in view, the various predisposing factors have been investigated.

Age Incidence.

Tuberculous meningitis is a disease which shows a definite predilection for the early years of life.

The age distribution in this series of 213 cases is shown on the accompanying table and graph. (See Pages 4 and 5)

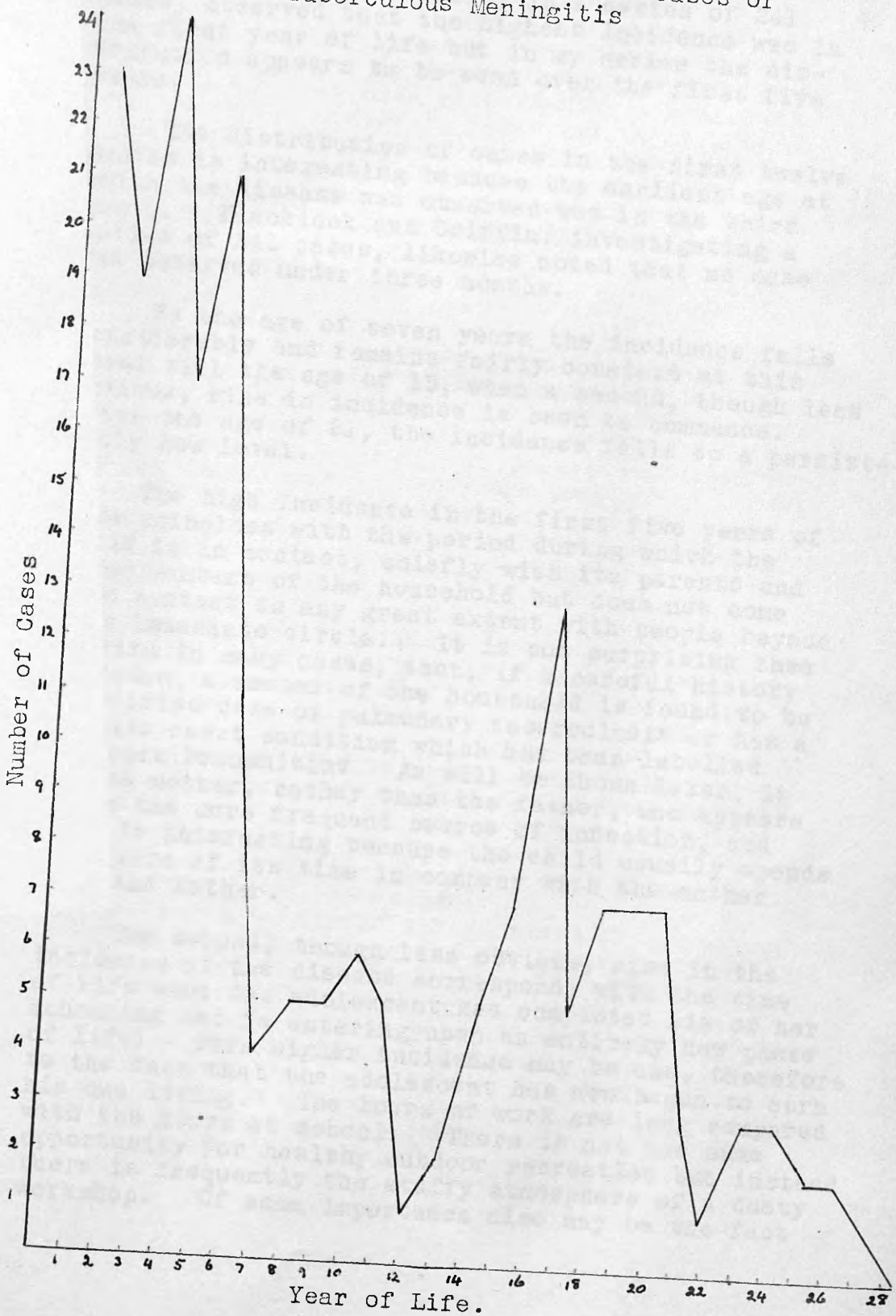
These figures represent the age distribution of all cases of tuberculous meningitis admitted to Belvidere Fever Hospital from 1936 to 1940 inclusive.

It will be seen that more than 50% of the cases occur during the first five years of life. The incidence is fairly constant during this period after which there is a rapid drop.

Age Distribution in a Series of 213 Cases of Tuberculous Meningitis.

Year of Life	Number of Cases
1st	23
2nd	19
3rd	24
4th	17
5th	21
6th	11
7th	4
8th	5
9th	5
10th	6
11th	5
12th	1
13th	2
14th	5
15th	7
16th	13
17th	5
18th	6
19th	6
2oth	6
21st	3
22nd	1
23rd	3
24th	3
25th	2
26th	2
27th	1
28th	-
29th	1
30 and over	6

Age distribution in a series of 213 cases of Tuberculous Meningitis



Blacklock and Griffin, in a series of 241 cases, observed that the highest incidence was in the first year of life but in my series the distribution appears to be even over the first five years.

The distribution of cases in the first twelve months is interesting because the earliest age at which the disease was observed was in the third month. Blacklock and Griffin, investigating a series of 241 cases, likewise noted that no case was observed under three months.

By the age of seven years the incidence falls considerably and remains fairly constant at this level till the age of 15, when a second, though less obvious, rise in incidence is seen to commence. After the age of 21, the incidence falls to a persistently low level.

The high incidence in the first five years of life coincides with the period during which the child is in contact, chiefly with its parents and other members of the household but does not come into contact to any great extent with people beyond this immediate circle. It is not surprising then to find in many cases, that, if a careful history is taken, a member of the household is found to be a notified case of pulmonary tuberculosis or has a chronic chest condition which has been labelled "Chronic Bronchitis". As will be shown later, it is the mother, rather than the father, who appears to be the more frequent source of infection, and this is interesting because the child usually spends much more of its time in company with the mother than the father.

The second, though less obvious, rise in the incidence of the disease corresponds with the time of life when the adolescent has completed his or her schooling and is entering upon an entirely new phase of life. This higher incidence may be due, therefore to the fact that the adolescent has now begun to earn his own living. The hours of work are long compared with the hours at school. There is not the same opportunity for healthy outdoor recreation but instead there is frequently the stuffy atmosphere of a dusty workshop. Of some importance also may be the fact

that the person has now come into contact with a new set of people, his fellow-workers, in whose immediate vicinity he spends several hours daily and some of whom may be suffering from pulmonary tuberculosis. All these changes take place in the average child's life about the age of 14 years and it is interesting to note that the peak incidence in this second rise is in the 16th year of life, just about the time when one would expect the various factors mentioned to be exerting their undermining influence.

Sex Incidence.

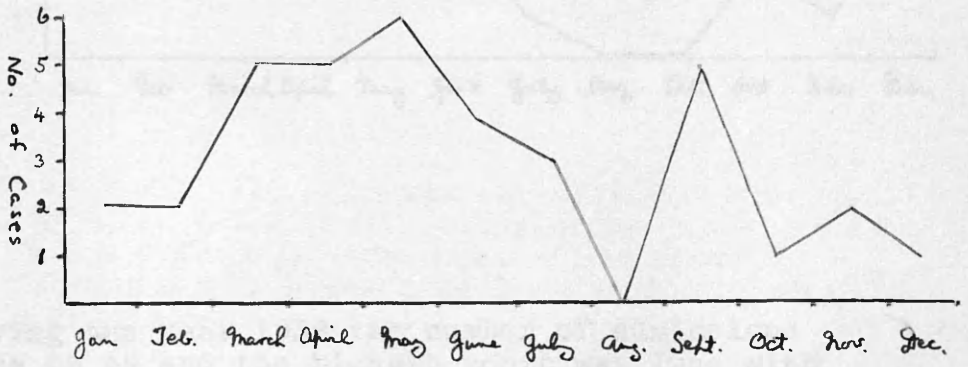
The sex incidence could not be studied from the series of cases under review because of an element of selection in the cases. In administering admission to hospital of cases of meningitis in Glasgow an attempt is made as far as possible to reserve one hospital for male cases and another for female cases. This, however, does not apply to young children but nevertheless the effect has been to give a definite bias to the male population in this particular instance.

To overcome the difficulty of selection of cases the statistics for the entire city of Glasgow were used as an alternative and this gave the added advantage of larger numbers and consequently the possibility of a more accurate estimate. The total number of cases of tuberculous meningitis during the ten year period, 1930 to 1939 inclusive, amounted to 1519. Of these, 781 cases were males and 738 were females giving percentages of 51.5 and 48.5 respectively. McCracken refers to a slightly higher incidence of males and states that the whole of this excess is due to deaths taking place in the age-group 0 - 4 years. Brown, on the other hand, states that the sex incidence is equal up to the age of three years and thereafter male cases predominate. This, he considers, is due to the fact that boys have more falls than girls, suggesting that injury to the head is a feature in the etiology. One point that I consider must be remembered, when trying to explain this slightly greater frequency in males, is the relative proportion of male to female births. Currie states that the proportion of male to female births is in the ratio of 104 to 100, so that at

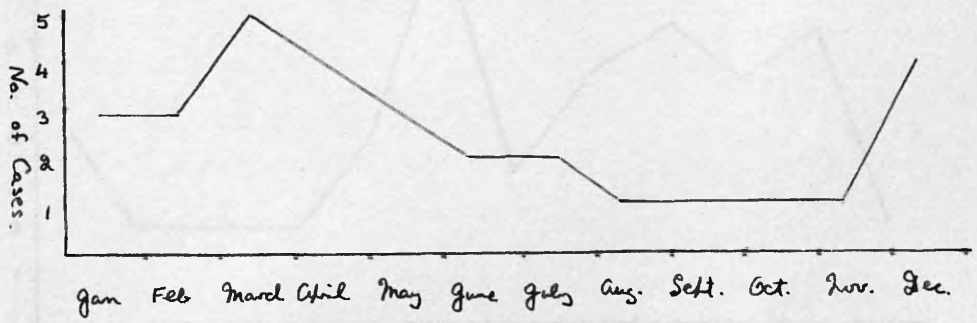
early ages there is a greater number of males than females exposed to the risk of infection, and consequently one would expect a somewhat higher incidence in males. This, I consider, explains partly, if not entirely, the slight disproportion between the two sexes.

Seasonal Incidence.

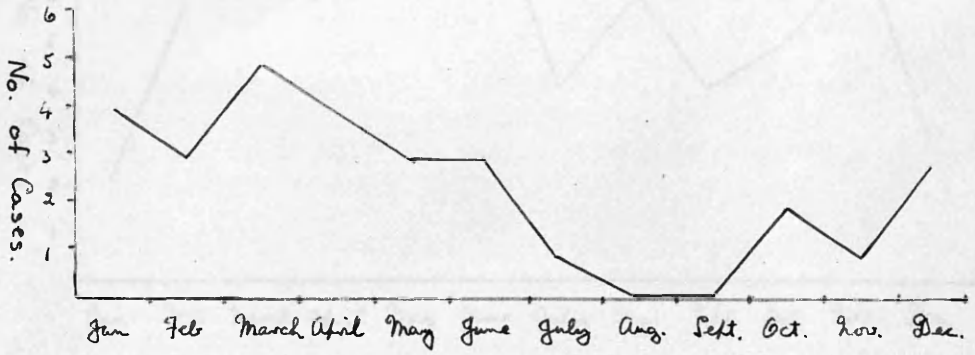
The number of cases of tuberculous meningitis admitted to hospital was observed month by month during the period 1936 to 1940 inclusive. In the year 1936 there were 36 admissions and the highest number reached was 6 in the month of May.



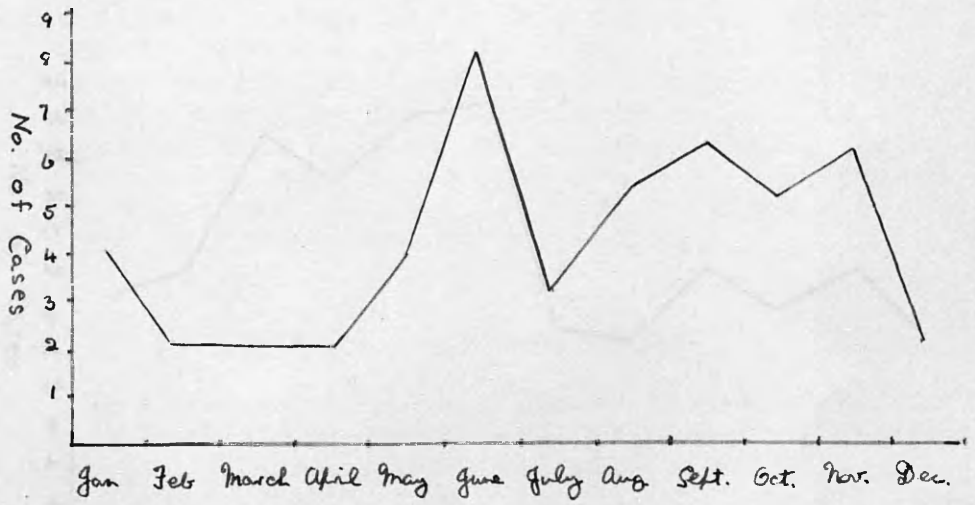
In 1937 there were 29 admissions and the highest was in March when 5 cases were admitted.



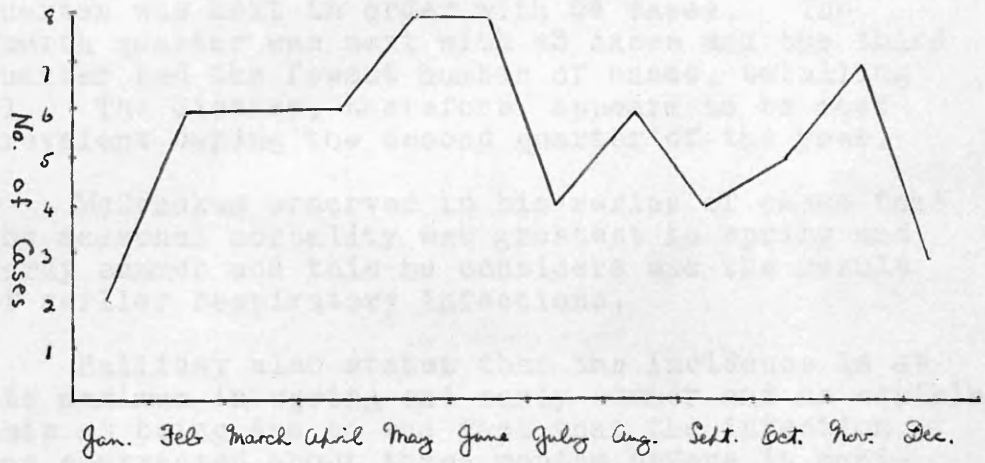
In 1938 the total number of admissions was 29 and March again was highest with 5 cases.



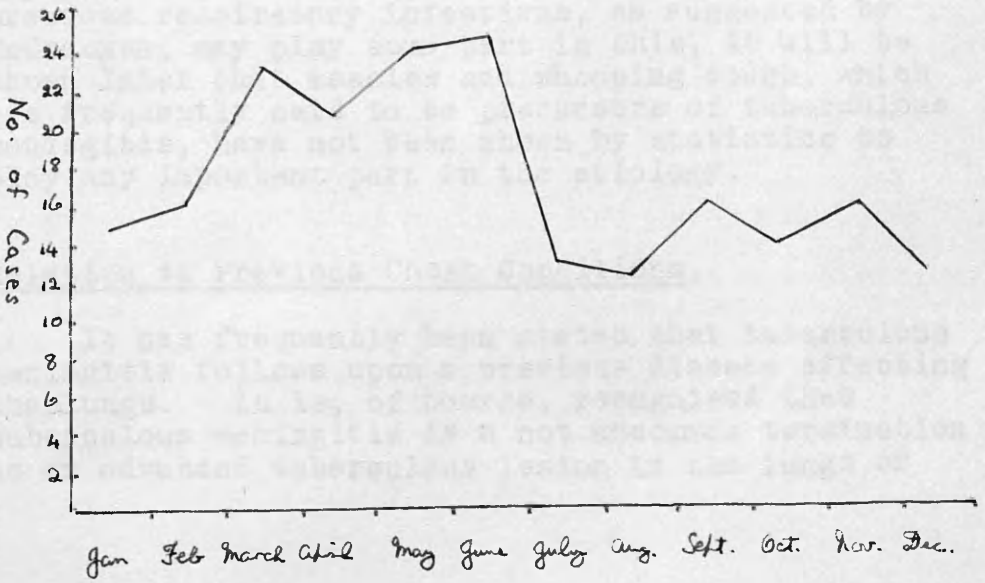
During the year 1939 the number of admissions rose to 49 and the highest month was June with 8 cases.



In 1940 the number of admissions again showed a rise to 65 and the peak months were May and June, each with 8 cases.



Each year with the exception of 1939 shows a tendency for the highest incidence to range around the first and second quarters. The number of yearly admissions however is a small figure on which to base statistics but if the total number of admissions for the five year period is considered according to the month of admission, it is seen that the largest number of cases occurs in the months of June, May, March and April in descending order of frequency.



Considering the admissions for each quarter of the year for the five year period 1936 to 1940 inclusive it is found that the second quarter of the year was highest with 70 cases. The first quarter was next in order with 54 cases. The fourth quarter was next with 43 cases and the third quarter had the fewest number of cases, totalling 41. The disease, therefore, appears to be most prevalent during the second quarter of the year.

McCracken observed in his series of cases that the seasonal mortality was greatest in spring and early summer and this he considers was the result of earlier respiratory infections.

Halliday also states that the incidence is at its maximum in spring and early summer and he explains this as being due to the fact that the infection was contracted about three months before it manifested itself clinically. If this is so, then the time when the disease is most frequently contracted is during the winter months, a time when infection of a respiratory nature is naturally most prevalent.

Blacklock and Griffin observed the same high incidence in the second quarter of the year. In their series of cases, the highest month was June, followed by April while May took third place. The lowest incidence for the year was seen in November.

The explanation for this high incidence in the second quarter seems to be best explained by the hypothesis put forward by Halliday. Although previous respiratory infections, as suggested by McCracken, may play some part in this, it will be shown later that measles and whooping cough, which are frequently said to be precursors of tuberculous meningitis, have not been shown by statistics to play any important part in the etiology.

Relation to Previous Chest Conditions.

It has frequently been stated that tuberculous meningitis follows upon a previous disease affecting the lungs. It is, of course, recognised that tuberculous meningitis is a not uncommon termination to an advanced tuberculous lesion in the lungs or

elsewhere in the body but this series of cases is interesting because in only 5 cases was a diagnosis of tuberculosis made before the onset of meningitis. Three of these were cases of pulmonary tuberculosis, one was a case of tuberculosis of the lungs and knee joint, and the fifth was a case of tuberculous disease of the kidney.

In the remaining 208 cases all but 15 were apparently in perfect health until the onset of the meningitis. Measles and whooping cough are sometimes blamed for the onset of this condition and in this series, six cases out of the above 15 exceptions had measles and subsequent chest complaints which terminated finally in the onset of tuberculous meningitis. Two cases were shown to be directly associated with whooping cough.

In these six cases, the onset of measles varied from four months to six weeks prior to the appearance of the meningeal symptoms and in two of these instances the children were under observation in hospital from the onset of the attack of measles until death took place from meningitis.

Of the seven remaining cases, tuberculous meningitis was the terminal phase of pneumonia in three, pleurisy in two and influenza in two.

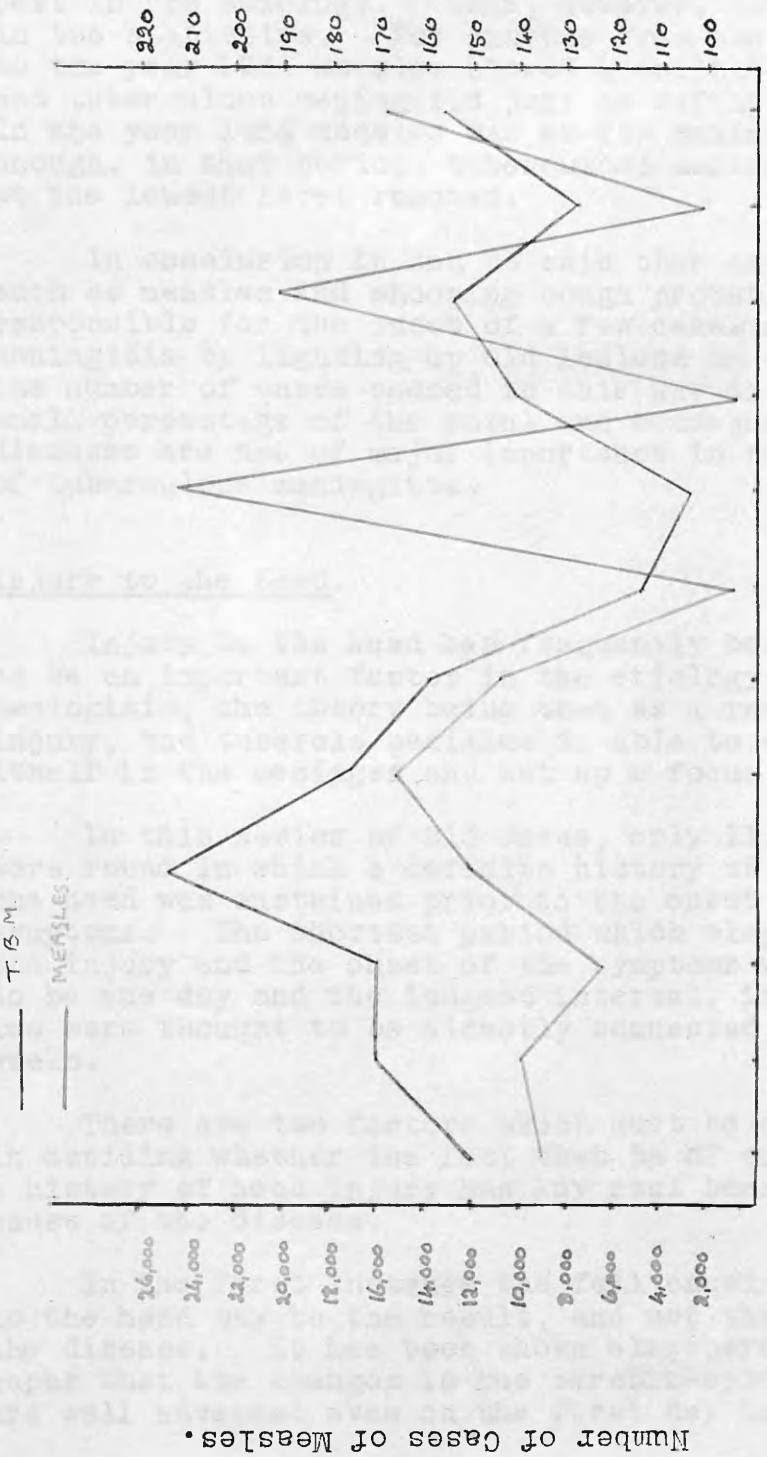
Those who attribute tuberculous meningitis to a previous attack of measles or whooping cough have suggested that these acute infections are responsible for lighting up a latent tuberculous lesion in the body and that this sometimes terminates in an involvment of the meninges. This theory has been confirmed to some extent by the above cases but at the same time it would appear that measles and whooping cough must play a very small part in the etiology of tuberculous meningitis. Measles was found to be directly associated with it in six cases only, in a series of 213, which represents a figure of 2.8%. Whooping cough was even less important, causing only two cases in 213, or .9%. These are very small percentages in view of the fact that more than half of the population have had measles at some time during childhood and fully one third have had whooping cough.

If measles was a factor of any importance in the etiology of tuberculous meningitis, then the annual variation of measles should have some influence on the annual incidence of tuberculous meningitis.

This point was investigated by charting the incidence of measles in Glasgow from 1927 to 1938 and the incidence of tuberculous meningitis over the same period.

Year	No. of cases of Measles	No. of cases of Tuberculous Meningitis.
1927	8983	150
1928	10098	170
1929	6468	171
1930	12004	214
1931	15372	177
1932	11000 approx.	160
1933	944	115
1934	24607	103
1935	893	140
1936	20196	155
1937	2272	127
1938	15839	157

See next page for corresponding graph.



Incidence of Measles and Tuberculous Meningitis in Glasgow from 1927 to 1938.

During periods when measles is prevalent one would expect an increase in the incidence of tuberculous meningitis if measles played an important part in the etiology. This, however, is not shown in the statistics. For example from the year 1930 to the year 1931 measles showed a definite increase and tuberculous meningitis just as definite a decrease. In the year 1934 measles was at its maximum and oddly enough, in that period, tuberculous meningitis was at the lowest level reached.

In conclusion it can be said that acute diseases such as measles and whooping cough probably are responsible for the onset of a few cases of tuberculous meningitis by lighting up old lesions in the lung but the number of cases caused in this way is only a very small percentage of the total and consequently these diseases are not of major importance in the etiology of tuberculous meningitis.

Injury to the Head.

Injury to the head has frequently been stated to be an important factor in the etiology of tuberculous meningitis, the theory being that as a result of the injury, the tubercle bacillus is able to establish itself in the meninges and set up a focus of infection.

In this series of 213 cases, only 11, or 5%, were found in which a definite history of injury to the head was sustained prior to the onset of meningeal symptoms. The shortest period which elapsed between the injury and the onset of the symptoms was stated to be one day and the longest interval, in which the two were thought to be directly connected, was five weeks.

There are two factors which must be considered in deciding whether the fact that 5% of cases giving a history of head injury has any real bearing on the cause of the disease.

In the first instance the fall causing injury to the head may be the result, and not the cause, of the disease. It has been shown elsewhere in this paper that the changes in the cerebro-spinal fluid are well advanced even on the first day in which the

clinical signs are present, and therefore presumably the injuries to the head, occurring in the few days prior to the onset of symptoms, actually occurred after the disease had become established and consequently these injuries can have no bearing on the etiology.

The second factor to be kept in mind is that children in health are frequently having falls and the head often comes in for some hard knocks so that some of the injuries to the head are probably due to coincidence and are quite unrelated to the subsequent onset of tuberculous meningitis.

If allowance is made for the fact that the disease may be present before the injury to the head and also for the possibility that the injury and the onset of disease are only a matter of coincidence, then injury to the head appears to play an extremely small part, if any, in the etiology of tuberculous meningitis.

Family History of Tuberculosis.

In each case, in this series, an inquiry was made as to whether any member of the family with whom the patient had been in contact, was suffering from tuberculosis. This line of investigation had not been pursued for long before it was realised that the results were not reliable. In several cases it was stated that no tuberculosis was present in the family and afterwards it was discovered from records that there was a notified case in the same household and on a few occasions the notified case turned out to be one or other of the parents.

For this reason it was decided to investigate the problem from another angle. By means of records of notified cases kept at the Public Health Department any person who was a notified case and who was living in the same household could be traced. A total of 205 families was investigated in this way and in 45 of these one or more members of the household were found to be notified cases.

Sixty four cases in all were traced in a total

or 45 families.

32	families	had	1	notified case.
9	"	"	2	" cases.
2	"	"	3	" "
2	"	"	4	" "

Fifteen of the notified contacts were notified to the local authority after the death of the patient suffering from tuberculous meningitis and these were discovered in most cases as a result of routine investigation carried out at the tuberculosis dispensaries.

Of the 45 families in which a tuberculous history was traced, 37 contained one or more pulmonary cases and in the remaining 8 families the disease was of a non-pulmonary nature.

Patient	Notified Contacts	Site of Lesion	Sputum
A. L.	Sister	Spine	
E. McM.	Uncle	Lungs	+ve
	Uncle	Lungs	+ve
A. H.	Sister	Meninges	
H. H.	Mother	Lungs	+ve
I. H.	Aunt	Lungs	+ve
	Aunt	Lungs	+ve
G. G.	Brother	Abdomen	
J. M.	Sister	Lungs	
G. C.	Aunt	Lungs	+ve
M. D.	Mother	Lungs	+ve
	Aunt	Lungs	+ve
	Aunt	Lungs	+ve
R. F.	Brother	Finger	
J. G.	Mother	Lungs	+ve
T. McC.	Mother	Lungs	+ve
T. McC.	Sister	Lungs	+ve
J. McG.	Brother	Meninges	-
A. W.	Sister	Lungs	-ve
J. C.	Mother	Lungs	+ve
W. B.	Father	Lungs	+ve
R. B.	Sister	Meninges	
	Brother	Lungs	
D. McP.	Mother	Lungs	-ve
	Brother	Lungs	

Patient	Notified Contacts	Site of Lesion	Sputum
J. W.	Brother	Meninges	
	Mother	Lungs	+ve
F. McE.	Father	Lungs	+ve
B. A.	Brother	Lungs	+ve
L. C.	Brother	Abdominal Wall	
N. L.	Mother	Lungs	+ve
W. B.	Father	Lungs	+ve
	Mother	Lungs	+ve
J. C.	Aunt	Lungs	
	Uncle	Lungs	
A. O'D.	Uncle	Lungs	
S. G.	Father	Lungs	+ve
J. O'H.	Father	Lungs	+ve
M. B.	Sister	Miliary	
J. S.	Father	Lungs	
	Brother	Lungs	+ve
	Brother	Abdomen	
	Sister	Lungs	
A. R.	Sister	Lungs	+ve
	Sister	Lungs	+ve
	Sister	Lungs	
	Brother	Lungs	
A. D.	Sister	Lungs	+ve
J. R.	Mother	Lungs	+ve
C. O'N.	Brother	Lungs	
T. T.	Mother	Lungs	+ve
J. D.	Sister	Lungs	
A. H.	Brother	Lungs	
	Sister	Lungs	+ve
	Brother	Abdomen ? Lungs	
B. McM.	Mother	Lungs	+ve
	Aunt	Abdomen	
E. McL.	Mother	Lungs	+ve
R. M.	Aunt	Knee	
W. M.	Father	Lungs	+ve
N. F.	Mother	Lungs	
A. B.	Sister	Lungs	+ve
	Brother	Lungs	
J. G.	Mother	Lungs	+ve

In 14 instances it was shown that the probable source of infection was the mother and in 6 cases only was the source traced to the father. In one family both the mother and the father were notified cases of pulmonary tuberculosis. The most probable explanation of this disparity is that the majority of cases of tuberculous meningitis occur in young children and children are in contact with the mother for much longer periods in the day than they are in contact with the father; consequently the mother features more frequently as the source of infection.

It has been shown that 37 cases of tuberculous meningitis, i.e., 18% of cases, were known to have been in contact with notified cases of pulmonary tuberculosis although they themselves did not show any evidence of tuberculous infection until the onset of the meningitis. This figure alone is significant in relation to the source of infection but at the same time it must also be remembered that a certain number of cases have probably been in contact with unrecognised cases of pulmonary tuberculosis which were not notified

Kinnear also investigated family contacts in a large series of cases and he was able to trace a family history of tuberculosis in 34% of the cases.

In conclusion it may be assumed from these results that contact with a case of pulmonary tuberculosis in the same household is a very definite factor in the etiology of tuberculous meningitis. This being the case, it would be expected that any rise in the incidence of pulmonary tuberculosis in the community would be accompanied by a corresponding rise in the incidence of tuberculous meningitis. Laidlaw and MacFarlane, in a recent article, have pointed out the increase which has taken place in the incidence of pulmonary tuberculosis in Glasgow in the last two years.

The increased incidence was based on the number of new notifications for the year.

For corresponding table, see over.

CITY OF GLASGOW

Year	No. of Notifications of Pulmonary Tuberculosis	No. of Cases of Tuberculous Meningitis admitted to Belvidere
1936	1647	36
1937	1654	29
1938	1748	29
1939	1574	49
1940	1908	65

The increased incidence of pulmonary tuberculosis took place in the year 1940 and a forecast for 1941 based on the returns for the first half of the year shows a still greater increase to 2190 new cases. Tuberculous meningitis figures, based on hospital admissions, also show a marked increase but it is interesting to note that this was first seen in 1939 and became more obvious in 1940. It is fair to assume that the increase of pulmonary tuberculosis was probably also present in 1939 but due to the difficulties of diagnosis in the early stages, most of these cases would not be notified until the following year.

The rise in the incidence of tuberculous meningitis and of pulmonary tuberculosis is undoubtedly one of the necessary evils associated with war. At the outbreak of war, and even before this, it was found necessary to reserve beds for possible casualties and in many cases such accommodation was obtained in large sanatoria. The immediate result of this was that large numbers of open cases of pulmonary tuberculosis were treated at home when normally they would have been removed to hospital. The presence of open cases of phthisis in overcrowded houses has resulted, therefore, in an increase of tuberculous meningitis and, as Laidlaw and MacFarlane have shown, an increase in the notification of pulmonary tuberculosis chiefly among young adults.

Conclusion

1. Tuberculous meningitis is a disease affecting chiefly children and young adults. In many cases young children develop the disease because of intimate contact with cases of pulmonary tuberculosis in the family. A rise in the incidence about the 15th year of life appears to be connected with the change in the mode of living when the adolescent leaves school and starts work in factories, etc.

2. The sex incidence shows a slightly higher proportion of males probably due to some extent to the fact that there is a slightly higher proportion of male than of female births.

3. The disease is more prevalent in the second quarter of the year.

4. Previous diseases involving the chest such as measles and whooping cough appear to play only a very small part in the etiology of the disease. Most cases are apparently in perfect health until the onset of the disease.

5. Injury to the head does not appear to be a factor of any importance in the etiology of tuberculous meningitis. Most of the cases of injury to the head can probably be attributed either to coincidence or to the early effects of the disease causing the child to lose its balance.

6. The most important factor in the etiology is contact with a case of pulmonary tuberculosis and this frequently takes place within the patient's own family circle.

SECTION II.

PATHOLOGY OF TUBERCULOUS MENINGITIS.

Autopsies were carried out on a series of cases for three primary reasons.

1. To confirm the diagnosis arrived at clinically and by examination of the cerebro spinal fluid.
2. To confirm the opinion that Tuberculous Meningitis is not a primary lesion but is secondary to some pre-existing tuberculous lesion in the body.
3. To study the pathological changes brought about by tuberculous meningitis on the Central Nervous System.

In this section the typical appearances of the central nervous system in tuberculous meningitis are described. The primary lesion in the body is considered from the point of view of the frequency with which it is found and its location. The association between tuberculous meningitis and miliary tuberculosis is discussed. The section concludes with the consideration of the most recent views as to the pathological processes at work in tuberculous meningitis.

Thirty eight post mortem examinations were carried out and the pathological changes in the central nervous system were more or less uniform, varying only in degree in different cases.

Central Nervous System.

When the skull cap was removed, in the majority of cases some flattening of the cerebral convolutions was observed together with congestion of the surface blood vessels. The most marked changes were usually to be found at the base of the brain. In this region a yellowish mucoid exudate had collected and the leptomeninges were thickened. Tubercles were found most frequently at the base of the brain and along the course of the superficial blood vessels especially in the region of the Sylvian fissure and between the frontal lobes. A small pressure cone was often present on the under surface of the cerebellum.

The ventricles were found to contain an excess of cerebro spinal fluid and tubercles were frequently observed on the choroid plexus. In ten cases tuberculomata were found in the substance of the brain tissue. In several instances these were multiple and varied from the size of a pea to that of a walnut.

Primary Lesion.

Careful search was made in each case for the presence of a pre-existing tuberculous lesion and in all but three cases this was shown to be present. The commonest site was found to be in the lung. This was seen in 13 cases and in most of them, the lesion was a small inactive nodule in the apical region of the lung with associated enlargement and caseation of the lymph glands in the lung root.

In 10 cases the mediastinal lymphatic glands were found to be tuberculous but no obvious lesion could be found in the lungs. In 2 cases a lung lesion was present with, in addition, tuberculous involvement of the mesenteric glands. 3 cases were found to have involvement of both the mediastinal and mesenteric glands. In 2 cases tuberculous ulceration of the bowel was present and in 3 cases the mesenteric glands alone were involved. The primary lesion in one case was found to be tuberculosis of the ovary and tube and in another case tuberculous cervical glands were the only source found.

Of the 38 cases examined only 3 failed to show a primary lesion elsewhere in the body and of these, two were found to have tuberculomatous masses in the brain substance which must have been present before the onset of the meningitis and which could therefore be considered to be the primary lesions. This leaves only one case in which no pre-existing lesion was found.

Association of Miliary Tuberculosis with Tuberculous Meningitis.

In many cases miliary tubercles were found in other organs of the body in association with the meningitis. The lungs were commonly found to be studded with numerous tubercles and, in the same way, the spleen was commonly found to be involved. Less frequently, tubercles were found on the surface of the liver and

kidneys and occasionally the peritoneum was involved. In several cases, however, although the meningeal lesion was well marked, no evidence of miliary tuberculosis could be discovered elsewhere in the body.

The relationship of tuberculous meningitis to miliary tuberculosis is one which still appears to be unsettled. At one time it was believed that tuberculous meningitis was part of a general miliary tuberculosis but at post mortem examinations it has been shown that tuberculous meningitis can be present without any evidence of a miliary involvement and in the same way, miliary tuberculosis can be present without meningitis. In this series, nine cases of tuberculous meningitis were examined at post mortem in which no evidence of miliary lesions elsewhere could be found.

Rich and McCordock investigated the origin of tuberculous meningitis and they came to the conclusion that meningitis did not result from a haematogenous spread but originated by direct spread from an adjacent pre-existing tuberculous focus. Such a focus could be in the meninges, in the substance of the brain or cord, in the choroid plexus, or in the bones encasing the central nervous system. Such a focus was found most frequently in the substance of the brain in close proximity to the meninges. These foci were believed to result from an early dissemination of the bacilli occurring about the time of the primary infection.

Rich and McCordock hold the view that the number of tubercle bacilli set free in the subarachnoid space in miliary tuberculosis is very small and not capable of producing the exudative reaction of tuberculous meningitis, although capable of producing circumscribed tubercles in the meninges and brain. They believe that the pre-existing focus in the brain, meninges, or bones surrounding these, is necessary, from which large numbers of bacilli can escape into the subarachnoid space. These authors base their opinions on the fact that of 77 cases of tuberculous meningitis examined at post mortem, in 75 instances were they able to show a pre-existing focus in the brain or cord, meninges, choroid plexus or bone encasing the central nervous system.

Macgregor and Green, working on the same lines,

investigated 88 cases of tuberculous meningitis at post mortem. Antecedent foci were found in 78 cases, either in the central nervous system or surrounding bone, but only in 59 of these was there conclusive proof that the focus was the source of the meningitis. These workers also tried to correlate their findings with the older theory that the meningitis was part of a generalised miliary condition but found that in 8 cases, miliary tuberculosis was absent, in 7 cases miliary tuberculosis was slight, and in 8 cases only was it severe and likely to have been the cause of the meningitis.

In conclusion, these workers state that the proportion of cases in which meningitis was traced to a local antecedent source was not as high as that of Rich and McCordock, but that their figures certainly support this conception.

Blacklock and Griffin state that they are also in general agreement with the conception put forward by Rich and McCordock but they consider that two points are not fully explained. First of all there is the frequent association of miliary tuberculosis with tuberculous meningitis and secondly the fact that in some cases of miliary tuberculosis without meningitis, tubercles have been observed in the choroid plexus.

Although neither Macgregor and Green nor Blacklock and Griffin give any definite opinion, it appears that both groups of workers support the conception of a local antecedent lesion with the reservation that probably a certain number of cases do arise directly from a miliary blood spread.

My own findings would certainly fit in with this compromise. In 10 cases out of 38, local antecedent foci in the form of tuberculomata were found. This relatively low proportion is probably explained by the fact that minute examination of the brains was not carried out and therefore small tuberculomata would escape unnoticed. In 9 of the cases, no evidence of miliary tuberculosis was found associated with the meningitis, and this certainly suggests that tuberculous meningitis is not always part of a miliary infection. In several cases, however, the accompanying miliary tuberculosis was quite extensive and advanced and in

these cases it is difficult to see why the meningitis is not part of the general infection.

SECTION III.

SIGNS AND SYMPTOMS OF TUBERCULOUS MENINGITIS.

In this section the signs and symptoms of most value in arriving at an early diagnosis are considered in detail. Mention is also made of the main features seen later in the disease when the diagnosis is on clinical grounds is obvious. The tuberculine skin tests are considered in relation to their value in diagnosis, and radioscopic examination of the chest is considered from the point of view of discovering a primary focus of tuberculosis.

Tuberculous meningitis is insidious in its onset and, in the early stages, the signs and symptoms are frequently so vague that a diagnosis on clinical grounds alone is not possible with any degree of accuracy. Certain sypmtoms are, however, suggestive of this disease in its early stages and these will be reviewed in their order of importance with an indication of the frequency with which they were observed to occur.

General Malaise.

The history showed that general malaise was invariably present before the onset of any definite symptom in the vast majority of cases. The mother frequently described the child as "off colour" or "hanging". This state, however, is frequently not well marked and consequently it is easily overlooked at the time.

Headache.

This is a most important symptom and is a fairly constant feature complained of in patients over three years of age. Below this age the symptom does not feature to the same extent bacause the child is too young to express this complaint. In young patients, however, the presence of headache can frequently be inferred by the restless state and rolling of the head on the pillow. This symptom was observed in 71% of cases over two years as one of the first indications of disease.

Vomiting.

This is a fairly constant symptom complained of early in the disease. Sickness in association with headache appears to be the first indication in most cases that all is not well with the child and makes the parents seek medical advice. Vomiting, however, is not always a feature: a few cases were observed in which there was no vomiting from start to finish of the condition.

It is also interesting to note that vomiting, although fairly constant early in the disease, was not observed to any great extent once the condition had become established, the vast majority of patients not showing this symptom from the time of admission to hospital till death supervened. Vomiting, as one of the first symptoms, was observed in 72% of all cases.

Abdominal Pain.

Pain in the abdomen was a symptom complained of in 13% of cases. Clinically, no abnormality was discovered on abdominal examination and the pain was probably of a referred nature. It was the first symptom complained of in several cases but was of short duration and was never of a severe nature.

Constipation and Diarrhoea.

Constipation was found to be a common accompaniment of the disease but diarrhoea was sometimes observed especially in young children. In this series 22% of children under four years of age were found to have enteritis as one of the earliest symptoms.

Convulsions and Twitching.

In a certain number of cases, the first indication of disease was the onset of a convulsive seizure. Convulsions, accompanied by twitching, were found in 13% of cases and these were for the most part children under three years of age. The twitchings were seen most frequently in the limbs but in a few cases, the muscles of the face, eyelids and tongue were affected.

Other Symptoms.

Less frequently, the earliest symptom observed took the form of pains in the arms or legs. In a few cases retention of urine was a complaint early in the disease but this was only seen in adults.

Late Symptoms.

Delirium is a symptom which was seen chiefly in older children and adults; it was of short duration because the patient passed rapidly into the drowsy state which is characteristic of the terminal stage of the disease.

Paralysis was seen in various forms during the course of the disease. The commonest forms seen were paralysis of the eye muscles causing strabismus, ptosis and inequality of the pupils. Paralysis of the limbs was sometimes seen in the intermediate stage but, like all the other forms of paralysis, it was not a common feature.

Drowsiness ushers in the terminal stage of the disease. It was a constant feature and varied greatly in duration but increased in degree until the patient passed into a state of coma, prior to death.

Kinnear investigated the frequency of the various symptoms in a large series of cases. He noted the symptoms which each patient presented on admission to hospital and placed them in the following order of frequency.

Vomiting was present in 89% of cases.
Constipation was present in 81% of cases.
Headache was present in 80% of cases over two years of age.
Strabismus was present in 31% of cases.
Stiffness of the neck was present in 65% of cases.
Kernig's sign was positive in 51% of cases.
Head retraction was present in 35% of cases.
Babinski's sign was positive in 31% of cases over two years of age.
Screaming was present in 29% of cases.
Convulsions were present in 29% of cases.

The knee jerks were absent in 27% of cases.
The abdominal reflexes were absent in 20% of cases.
Twitching was observed in 15% of cases.

It will be seen from an analysis of the symptoms in the series observed by Kinnear, and also in my own series, that the main features early in the disease are headache, vomiting and constipation, together with nuchal rigidity and a positive Kernig's reaction.

Examination of the Patient.

Very often the history is of more value in diagnosis than the signs made out at clinical examination. Tuberculous meningitis, however, like other forms of meningitis, causes irritation of the meninges and spasm of certain muscles. The spasm of the muscles is seen in the rigidity of the neck and can also be recognised by the presence of Kernig's sign.

Nuchal Rigidity.

To perform this test the patient is lying flat on the back. If nuchal rigidity is present, any attempt to flex the head forwards on to the chest is resisted by the patient and if the head is forcibly flexed, the bending is accompanied by severe pain. This is a useful sign of meningeal irritation and is present in most cases of tuberculous meningitis. It is not usually so well marked as in the various types of acute meningitis and in a number of cases it was found to be entirely absent early in the disease.

Kernig's Sign.

To test for the presence of this sign, the patient is placed flat on the back. The thigh is flexed almost to a right angle and the knee is extended, the other leg remaining flat on the bed. If there is rigidity, the hamstring muscles are thrown into spasm and the knee cannot be completely extended. This sign, like nuchal rigidity is a good indication of meningeal irritation but in tuberculous meningitis it was frequently found that it was not well marked and in a number of instances, the sign was quite

negative early in the disease.

Tendon Reflexes.

The tendon reflexes were found to be of no real value in diagnosis. The knee jerks were found in most instances to be normal but were occasionally increased or absent. The plantar reflex, though usually flexor, gave no response in some cases and in young children it gave the physiological extensor response.

Examination of the Eyes.

Helpful information may be obtained from examination of the eyes. There may be ptosis or twitching of the lids. Strabismus may be present, usually of the internal type, and in one case, conjugate deviation of the eyes to the right was observed. The pupils are usually equal in size but occasionally they are found to be disproportionate. Late in the disease, when the patient has passed into the terminal phase, the pupils become dilated.

Examination of the optic fields is said to be of diagnostic value because tubercles may be observed on the retina. The examination of the fundi was carried out systematically and early papilloedema of the optic nerve was frequently observed, indicating increased intracranial pressure. In one instance only were tubercles observed on ophthalmoscopic examination and this patient was also suffering from a generalised miliary spread of the tuberculosis.

As a diagnostic point, the presence of tubercles on the retina is conclusive of the nature of the disease but the condition was seen so seldom, in my experience, that it is of little value from the diagnostic point of view.

Search for the Primary Focus of the Disease.

In each case, search was made in the chest, abdomen, glands, bones and joints for the primary focus of the disease. In the majority of cases, no such focus was discovered because, as was seen later at

post mortem examinations, although such a focus was usually present, in the majority of cases it consisted of a small, apparently inactive lesion.

1. The Chest.

Usually, no evidence of tuberculosis was to be found on clinical examination although, in the later stages of the disease, moist rales were frequently heard due to hypostatic congestion. X-ray examination of the lungs was also carried out and lesions, which could not be detected clinically, were sometimes discovered by this method. The commonest lesion seen was enlargement of the root glands without any obvious lesion in the lungs. In a few cases, a small healed lesion was seen in the substance of the lung, usually situated at one or other apex. Advanced tuberculosis of the lungs was not commonly seen in this series of cases.

Several cases were seen in which the tuberculous meningitis was associated with a generalised miliary tuberculosis of the lungs and in these, the typical snowstorm appearance was observed. In the majority of cases, however, no lesion was observed and X-ray examination was not found to be of any great value in the diagnosis, except where it revealed miliary disease of the lungs.

Case of Miliary Tuberculosis.

The patient M.H., a female of 29 years of age, was admitted to hospital on 19.5.41. She was in her third week of illness and was complaining of loss of weight and weakness.
On admission she was very emaciate and pale.
Examination of the chest revealed the presence of a few scattered rales and rhonchi in both lungs. As a result of the clinical examination, a provisional diagnosis of miliary tuberculosis was arrived at.

The patient was X-rayed on 24.5.41 and no evidence of lung disease was observed on the plate. The temperature was of the swinging type and as a result of the negative X-ray examination, other lines of investigation were instituted. The Widal test was found to be negative for B. Typhosus and B. Paratyphosus. The blood was then tested for agglutination

against Br. Abortus but this also proved to be negative. The patient had no symptoms suggestive of meningeal irritation but a lumber puncture was performed because of a slight papilloedema seen when the fundi were exmained on 22.5.41.
The cerebrospinal fluid was clear and not under pressure. The only abnormality was an increase in the cell count to 37 per cu. mm. and these were chiefly lymphocytes.

On 31.5.41 the papilloedema was more definite but on this occasion the cerebro spinal fluid was normal in all respects. The chest was again X-rayed on 31.5.41 but no evidence of disease could be found. X-ray of the skull on the same day showed no abnormality.
The temperature remained intermittant and the patient failed to improve. The chest was again X-rayed on 21.6.41 but no disease was found to be present.

The fundi were examined regularly throughout the course of the disease and the papilloedema, although at no time gross, was always found to be present.
On 22.7.41 two small miliary tubercles were observed for the first time, one in each fundus, and X-ray of the chest on the following day showed a very early miliary tuberculosis to be present.
Throughout all this time no clinical signs or symptoms of meningeal irritation were present. Lumbar puncture on 24.7.41 again showed a fluid normal in all respects.

The chest was again X-rayed on 9.8.41 when a typical snowstorm appearance of the lung was found to be present.
The patient's condition gradually deteriorated from this date onwards and she died on 30.8.41.
Post mortem examination was not granted.

There are several interesting features in this case.

1. The total duration of the disease was 17 weeks. In the third week of illness the patient was clinically an obvious case of tuberculosis of a miliary type but the patient lived for a further 14 weeks.

2. Although the case was clinically one of miliary tuberculosis, on admission to hospital, the X-ray

examination of the chest at this date was negative. The X-ray of the chest was negative in the 4th week of illness and still negative in the 8th week of illness. Not until the 12th week was there evidence of early miliary tuberculosis. By the 14th week the condition in the chest was well marked on X-ray examination.

3. The fundi were examined regularly but tubercles did not make their appearance in the retina until the 12th week of illness.

4. As a result of the tubercles having been observed in the fundi, it can be assumed that the miliary condition was widespread and must have involved the central nervous system to some extent. Despite this, the cerebro spinal fluid which was examined on three different occasions showed none of the characteristics of the fluid in tuberculous meningitis and in actual fact, the only abnormality observed was a slightly increased lymphocyte count on the first occasion.

2. The Abdomen.

The abdomen was normal in the vast majority of cases. The scaphoid type of abdomen was frequently observed but only in a few instances was the enlarged, hard abdomen of tuberculous peritonitis observed.

3. Glands.

The cervical glands were found to be involved in one instance.

No case was observed in which the primary focus was seen in a bone or joint.

Skin Tests for Tuberculosis.

All patients showing clinical evidence of meningeal irritation were subjected to a Tuberculine Skin Test in order to investigate whether such tests would provide any additional help in separating out the tuberculous cases. Two tuberculine tests were used, the Mantoux Test and the Tuberculine Patch Test.

Mantoux Test.

For this test, Koch's Old Tuberculine diluted 1 in 1,000 was used. Into the skin of the forearm 0.1cc of the dilution was injected and the site of injection was examined after twelve, twenty four and forty eight hours respectively. A positive reaction was indicated by the development of a raised, red spot which enlarged from a diameter of, from $\frac{3}{8}$ of an inch to 1 inch. The maximum extent of the inflammation was usually reached in 48 hours.

This test was carried out on a series of 59 cases, all of which were showing symptoms of meningeal irritation. 24 of these cases proved to be suffering from tuberculous meningitis and the remaining 35 were of a non tuberculous nature, consisting of such conditions as lymphocytic meningitis, poliomyelitis, brain abscess and meningismus.

Out of 24 cases of tuberculous meningitis, 19 gave a positive reaction to the Mantoux Test and in 5 cases the test was negative. Even this short series, therefore, shows that all cases of tuberculous meningitis do not give a positive tuberculine skin test. Actually, only 79% of proved cases gave a positive skin reaction.

In the 35 non tuberculous cases, 11 gave a positive reaction and 24 gave a negative reaction. This represents a positive incidence of 31%.

It would appear from these results that the Mantoux Test is of practically no value from the point of view of diagnosis in tuberculous meningitis. If a positive result is obtained, this does not necessarily mean that the patient has tuberculous meningitis because, as has been shown, 3 cases in every 10 with meningeal symptoms due to disease of a non tuberculous nature gave positive skin reactions. On the other hand, if a negative result is obtained, this does not exclude the diagnosis of tuberculous meningitis because it has also been shown that 2 cases in every 10 suffering from tuberculous meningitis gave negative skin reactions.

Tuberculine Patch Test.

For this test, the Vollmer patch was used. This consists of a square of filter paper, saturated in tuberculine and placed on adhesive tape. In actual practice, two such squares are placed on each tape and between them is a control square which contains no tuberculine. To make the test, an area of skin over the sternum or along the upper spine is cleansed and defatted with acetone and the strip of adhesive is applied. The tape is left in position keeping the tuberculine squares in contact with the skin for 48 hours, then removed. The reading of the test is made 48 hours after the removal of the tape. A positive result is indicated by the appearance of sharply circumscribed, reddened squares where the tuberculine filter papers were in contact with the skin, but no redness of the area which the control square covered.

A series of 40 cases showing signs of meningeal irritation was subjected to the Tuberculine Patch Test, 17 of the cases being proved tuberculous meningitis and the remaining 23 were of a non tuberculous nature. Of the 16 cases of tuberculous meningitis tested, only 7 gave a positive result and 10 were negative.

In the non tuberculous group of cases, 5 were positive and 18 gave negative reactions.

From these results it would appear that the Tuberculine Patch Test, like the Mantoux Test, is of practically no assistance in the diagnosis of the condition because only 41% of proved cases of tuberculous meningitis gave a positive reaction, and, in addition, a positive result was obtained in 22% of non tuberculous cases.

The value of the tuberculine tests in the diagnosis of tuberculosis was investigated by McNeil and he states that a negative reaction in a diseased condition suggestive of tuberculosis, excludes a diagnosis of tuberculosis. This, however, has not been my experience with the Mantoux and Patch Tests in tuberculous meningitis, where a considerable number of proved cases have given a negative reaction. Ogilvie found the same state of affairs when, in the course of his investigations, he observed that the

tuberculine test in rapidly advancing disease of the chest and miliary tuberculosis, was frequently negative. Wilson states that a negative tuberculine reaction is no indication of the absence of tuberculosis and he gives two possible explanations. He observes that in infancy, sensitivity to tuberculine may not have yet developed and secondly, he points out that in advanced disease of any type, the reactive ability may be lost. If we assume these statements to be correct, then we have a possible explanation of why negative reactions in known cases of tuberculous meningitis are frequently found and, for this reason, I consider that tuberculine tests are of no assistance as an aid to the diagnosis of tuberculous meningitis.

Differential Diagnosis.

Tuberculous meningitis is simulated clinically by a variety of diseases, the chief of which are cerebro spinal fever and other forms of acute meningitis, brain abscess, poliomyelitis and encephalitis, lymphocytic meningitis, subarachnoid haemorrhage and meningismus, complicating such diseases as enteritis and pneumonia.

The chief feature of differentiation between tuberculous meningitis and these other conditions is the gradual onset of the symptoms. Headache, vomiting, nuchal rigidity and a positive Kernig's reaction are common to them all and indicate, at the most, the presence of meningeal irritation. X-ray of the chest may be of some value by showing the presence of a primary focus of tuberculous disease in the lungs. Miliary tuberculosis, if present, may give the typical snowstorm appearance. Examination of the optic fields may occasionally show the presence of tubercles in the retina.

Usually, however, early in the disease, after a thorough clinical examination, one can say no more than that tuberculous meningitis is a possible diagnosis and it is essential at this stage to seek further evidence by examining a specimen of the cerebro spinal fluid.

SECTION IV.

THE CEREBRO SPINAL FLUID IN TUBERCULOUS MENINGITIS.

Although it is frequently possible to diagnose tuberculous meningitis clinically in its later stages, it is extremely difficult to be certain from clinical signs alone, especially when the patient is seen early in the disease. For this reason it is essential to examine the cerebro-spinal fluid before a definite statement can be made. The disease is frequently simulated by such conditions as pneumonia, gastro-enteritis, convulsions, encephalitis, polio-myelitis, brain abscess and many other conditions causing meningeal irritation, but by a thorough investigation of the cerebro spinal fluid I consider it possible to rule out these conditions by differential diagnosis.

In a series of 42 cases of proved tuberculous meningitis the fluid was examined in detail. In all cases the fluid was withdrawn by lumbar puncture and in no case was it found necessary to resort to cisternal puncture. To serve as a control for this investigation all cases suggestive in any way of tuberculous meningitis were lumbar punctured and the fluid subjected to the same tests as the tuberculous fluids. In all, the control series consisted of 141 cases suffering from a variety of conditions other than tuberculous meningitis.

All fluids obtained at lumbar puncture fell into one of the following classes:-

1. Turbid.
2. Slightly turbid.
3. Clear.
4. Xanthochromic.
5. Blood stained.

Turbid Fluids.

When a turbid fluid was obtained, the specimen was centrifuged and films were made of the pus in the

deposit. In all cases polymorphonuclear cells were found to be greatly in excess and in most cases the causative micro-organism was observed in the film or was obtained after culture.

This group was composed entirely of cases of acute meningitis and the organisms isolated consisted of the meningococcus, the pneumococcus, the haemolytic streptococcus, the bacillus coli and in one case, the influenza bacillus. (See Table I.)

Table I - Turbid Fluids.

Organism isolated	Number of Cases investigated
Meningococcus	50
Streptococcus	1
Pneumococcus	2
Bacillus Coli	1
Bacillus Influenza	1

No example of tuberculous meningitis was found in which the fluid could be classed as turbid. For this reason any turbid fluid was examined according to the above routine and then excluded from the cases under investigation.

Routine Methods of Examination.

A. At the time of withdrawal of the fluid an opinion was expressed as to whether or not the pressure was increased.

B. The naked eye appearance of the fluid was noted. It may fall into one of the following groups:-

(a) Clear
(b) Slightly turbid
(c) Xanthochromic

C. The cell content was enumerated by means of the Fuchs-Rosenthal counting chamber.

D. The greater part of the sample was set aside to allow time for a web to form. The remainder of the sample was centrifugalised and a film made to examine the type of white cells present and to carry out a differential count.

E. After 24 hours the sample, previously set aside, was examined for the presence of a web. If present, the web was removed and spread out on a slide. The specimen was then stained by the Ziehl-Neelsen method to try if possible to demonstrate the presence of the tubercle bacillus.

F. The protein content of the fluid was then estimated. A variety of methods, both qualitative and quantitative were used in the present investigation.

G. The sugar content was estimated, both qualitatively and quantitatively.

H. The amount of chlorides present was investigated quantitatively.

I. The Tryptophan Test, which has been claimed to be diagnostic of tuberculous meningitis, was performed.

J. The Levinson Test, also said to be diagnostic of tuberculous meningitis, was carried out.

As a result of lumbar puncturing all cases showing any signs suggestive of tuberculous meningitis, 183 specimens of cerebro spinal fluid were obtained. After the exclusion of all turbid fluids by the method previously outlined, 128 fluids remained for more detailed examination. (See Table II).

The various investigations are discussed in the order previously outlined.

Table II - Clear or only Slightly Turbid Fluids.

Disease	Number of Cases investigated.
Tuberculous Meningitis	42
Brain Abscess	4
Tonsillitis	5
Otitis Media	1
Meningismus	5
Pneumonia	10
Miliary Tuberculosis	4
Lymphocytic Meningitis	10
Influenza	4
Poliomyelitis	9
Encephalitis	4
Subarachnoid Haemorrhage	5
Enteritis	3
Cerebro Spinal Fever (in process of recovery)	7
Tuberculoma	1
Tuberculous Broncho-Pneumonia	3
Whooping Cough	4
Posterior Basic Meningitis	1
Septicaemia	2
Subdural Abscess	1
Arterio Sclerosis	1
Teething	1
Cavernus Sinus Thrombosis	1

The Pressure of the Cerebro Spinal Fluid.

The pressure of the fluid can be ascertained by means of a manometer which is attached to the lumbar puncture needle. In the present investigation this method was not adopted because in most cases the patients were punctured without the use of a general anaesthetic and since the majority were children, struggling and resistance on the part of the patient were frequently encountered. To get a reliable reading with the spinal manometer the patient must be lying absolutely at rest. False readings are given by such conditions as variation in posture, crying, coughing, struggling and holding the breath.

Opinion as to whether the fluid was under increased pressure or not was expressed by observing the rate of flow of the fluid from a standard bore of lumbar puncture needle. In many cases the increase of pressure was obvious but in the majority it was difficult to assess and in reviewing my observations I have come to the conclusion that practically no value can be placed on this procedure unless in the adult at rest.

The Naked Eye Appearance of the Fluid.

No case of tuberculous meningitis was observed in which the fluid was classified as turbid. The vast majority of the cases showed perfectly clear fluids, a few showed very slight turbidity and 4 cases had xanthochromic fluids.

Clear Fluids.

Although the fluid obtained at lumbar puncture is clear it cannot be assumed that it is a normal fluid. The majority of cases of tuberculous meningitis observed were found to have clear cerebro spinal fluids. Other conditions observed in which the fluid was clear and the patient showed signs suggestive of tuberculous meningitis, included such conditions as meningismus, acute poliomyelitis, brain abscess and the so-called lymphocytic meningitis.

Slightly Turbid Fluids.

The turbidity of the cerebro spinal fluid is due to the presence of leucocytes. The cell content of the fluid may however be raised considerably above normal without obvious turbidity. When there are more than 400 leucocytes per cu. mm. in the fluid a slight degree of turbidity can usually be detected.

Several cases of tuberculous meningitis were observed to give a slight degree of turbidity in the fluid but other conditions such as brain abscess

and mild attacks of cerebro spinal fever gave a similar appearance.

Xanthochromic Fluids.

Xanthochromic fluids are interesting because if such fluid is obtained at lumbar puncture the tendency is to be satisfied that the diagnosis in the case is due to a haemorrhage into the subarachnoid space which is causing meningeal irritation. In my investigations however I observed four cases of tuberculous meningitis where the fluid was xanthochromic and these cases might have been wrongly diagnosed if a complete investigation of the fluid had not been carried out. Post mortem examination in two of these cases suggested that the cause of the xanthochromia was the congested state of the vessels on the base of the brain leading to rupture and haemorrhage into the subarachnoid space.

Other instances of xanthochromic fluids investigated in this series were cases of subarachnoid haemorrhage and one case of cerebral haemorrhage in which the blood had torn its way through the brain substance and entered the lateral ventricle.

It is clear then that the presence of xanthochromia in a fluid does not exclude a diagnosis of tuberculous meningitis and in all such fluids further investigation is essential.

Blood Stained Fluids.

Blood staining in the cerebro spinal fluid is due to one of two causes

(a) Bleeding into the subarachnoid space due to such conditions as cerebral haemorrhage or cerebral aneurysm.

(b) Trauma while carrying out the lumbar puncture. With experience this condition is seldom encountered but must always be considered as a possible occurrence. If such a specimen is obtained it is advisable to discard it and try again in the interspinous space above or repeat after 24 hours.

When the fluid was intimately mixed with blood and no question of trauma arose, the specimen was centrifuged. Usually the supernatant fluid was found to be xanthochromic and was retained for further investigation.

Cell Count.

The enumeration of the cells present in the cerebro spinal fluid is one of the chief means of detecting the presence of infection of the brain or meninges.

Method.

The cell count was estimated immediately after the fluid was withdrawn. The apparatus consisted of a pipette such as is used for counting the leucocytes in the blood, and the Fuchs-Rosenthal counting chamber. A solution of methylene blue in acetic acid* was drawn up to the mark 1 on the stem of the pipette and the cerebro spinal fluid was then drawn up till the mixture reached the mark 11. By rotating the pipette the solutions were mixed thoroughly and a small amount was then rejected. A drop of the remainder was then placed upon the counting chamber and the total number of cells within the ruled area was counted. This number divided by 3 gave the number of cells present in each cubic millimeter of cerebro spinal fluid.

The normal white cell count of the cerebro spinal fluid is stated to be from 0-6 cells per cu. mm. and, in my experience of examining a large number of normal fluids, the count always falls within these limits although, in the vast majority of cases, I found the count to be from 0-3 cells per cu. mm.

In disease involving the brain or meninges, the cell count usually becomes increased and the extent of this increase, together with the predominating type of cell, is of value in deciding the nature of the disease.

*Methylene Blue 1%, Acetic Acid 5%.

Table III - Cell Count in Tuberculous Meningitis.

Serial No. of Case	Cell Count per cu.mm.	Serial No. of Case	Cell Count per cu.mm.
1	309	22	133
2		23	347
3	65	24	180
4	850	25	133
5		26	51
6	500	27	
7	140	28	
8	118	29	379
9	288	30	600
10	41	31	133
11	134	32	412
12	260	33	220
13	427	34	46
14	75	35	117
15	350	36	175
16	170	37	
17	60	38	407
18	180	39	241
19	58	40	976
20	300	41	129
21			

The Cell Count in Tuberculous Meningitis.

See Table III above.

This was found to vary within fairly wide limits. The minimum count recorded was 41 cells per cu. mm. and in 3 cases only did the count exceed 500 cells per cu. mm. The maximum recorded count was 976 cells per cu.mm.

Giustra states on observations made in 10 cases of tuberculous meningitis that the cell count varied from a minimum of 76 cells to a maximum of 423 cells per cu. mm.

Clark , in a series of cases under review, states that the variation of cells was from 70 to 500 per cu.mm.

with one exception when a count of 1250 was recorded.

Stewart found the count in tuberculous meningitis to vary from 34 to 584 cells per cu. mm. in a series of 30 cases which he investigated.

Ingham investigated a series of 84 cases and found the cell count to vary from 20 to 1952 per cu. mm.

Kinnear found the average cell count in tuberculous meningitis to be 73 cells per cu. mm.

The type of cell present and its relative preponderance was estimated by carrying out a differential white cell count. A specimen of the cerebro spinal fluid was centrifugalised and a film made from the fluid at the foot of the centrifuge tube. The slide was stained with methylene blue and the relative percentages of polymorphs and lymphocytes counted.

The differential count in tuberculous meningitis showed a marked preponderance of lymphocytes in every case, varying from 75% to 100% of the total number of cells counted.

Giustra states that in his series of 10 cases, the lymphocytes were from 88% to 100% of the total.

Ingham states that the average lymphocyte count in his series was 82% and that the count was always over 50% lymphocytes.

Kinnear found the average lymphocyte count to be 88%.

Stewart observed that in his series of 30 cases the differential count showed from 80% to 98% lymphocytes to be present.

Clark, on the other hand, states that the average differential count in his series was 78% lymphocytes but one case showed lymphocytes and polymorphs to be present in equal numbers and three cases showed a preponderance of polymorphs.

I consider that the lymphocytes are always in excess in the cerebro spinal fluid of tuberculous meningitis and I have found that an increased cell

count where the lymphocytes predominate is a very important point in the diagnosis of tuberculous meningitis.

The cell count and differential count were also studied in diseases other than tuberculous meningitis for the purposes of differential diagnosis.

In septic meningitis and cerebro spinal fever the fluid is usually turbid and contains a very large number of cells which are chiefly polymorphs. Some difficulty may arise, however, where a mild case is lumbar punctured at the stage where it is beginning to clear up of its own accord. In such cases, the cell count frequently was found to fall within the limits expected in a case of tuberculous meningitis but when the differential count was carried out, the percentage of polymorphs was always very high, in some cases actually 100%.

Table IV. - Septic Meningitis.
(Cases of a mild type and clearing up).

Serial No. of Case	Cell Count per cu. mm.	Predominating Type of Cell.
1	46	P
2	900	P
3	590	P
4		P
5	430	P
6	456	P
7	709	P

In meningismus, a condition found most frequently in children associated with peumonia, gastro enteritis and other acute illnesses, the cell count was always within normal limits which differentiated the condition at once from tuberculous meningitis.

Lymphocytic meningitis showed an increase of cells which fell within the same limits as the cell count in tuberculous meningitis and the differential

count showed the same preponderance of lymphocytes that one would expect in tuberculous meningitis. In the 10 cases observed in my series of controls, the minimum count was 10 cells and the maximum was 309 cells per cu. mm. (See Table V.)

Table V. - Lymphocytic Meningitis.

Serial No. of Case	Cell Count per cu. mm.	Predominating Type of Cell.
1	96	L
2	10	
3	50	L
4	167	L
5	142	L
6	33	L
7	82	L
8	53	L
9	303	L
10	309	L

The cell count is therefore of no value in the diagnosis between these two diseases but as will be shown later, the two diseases could be differentiated by estimation of the protein, sugar and chloride count.

Brain abscess was another condition in which the cerebro spinal fluid showed a moderate increase in the cell count on occasions. The type of cell varied; in some cases polymorphs were in excess and in others lymphocytes predominated. (See Table VI.)

Table VI. - Brain Abscess.

Serial No. of Case	Cell Count per cu. mm.	Predominating Type of Cell
1	180	L
2	41	L
3	560	P
4	20	L

In poliomyelitis and encephalitis it was usual to find only a slight increase of cells but on occasions the count was found to be moderately high. The highest count observed was 240 cells per cu. mm. In these conditions the cells were found to be chiefly lymphocytes. (See Tables VII and VIII.)

Table VII - Poliomyelitis.

Serial No. of Case	Cell Count per cu. mm.	Predominating Type of Cell.
1	23	L
2	240	L
3	36	L
4	4	
5	12	
6	17	
7	33	L
8	18	
9	55	L

Table VIII - Encephalitis.

Serial No. of Case	Cell Count per cu. mm.	Predominating Type of Cell.
1	77	L
2	15	
3	25	L

In one case of cavernous sinus thrombosis some doubt arose as to the possibility of its being tuberculous meningitis when at lumbar puncture a slightly turbid fluid was obtained with a cell count of 225 per cu. mm. A differential count at once excluded tuberculous meningitis when 87% of the cells present were found to be polymorphs.

A Case of Cavernous Sinus Thrombosis.

A child, C.C., aged 4 years, was admitted to hospital on 28/5/41 with a provisional diagnosis of septic meningitis.
The history was that the child had complained of severe frontal headache and had been vomiting on 26/5/41 (i.e. 2 days prior to admission).
On 27/5/41 both eyelids became very swollen.

On admission the child was noted to be very ill and toxic.
The temperature was 103° F. and the pulse rate 104.
The patient was delirious.
Both eyelids were oedematous. The left orbit did not appear to be pushed forward and the right orbit could not be seen because of the oedema. There was no evidence of any septic lesion of the face.
The head was retracted and nuchal rigidity was present.
Kernig's sign was positive.
Chest and abdomen were normal.

The patient was lumbar punctured and a very slightly turbid fluid was obtained.
The cells numbered 225 per cu. mm., 87% of which were polymorphs.
The protein content was 40 mgm. per 100 cc.
The sugar was normal.
The chlorides were 670 mgm. per 100 cc.
The Levinson Test was negative.
No organisms were seen in the fluid.
The child died on 29/5/41 in its 4th day of illness.

At the post mortem examination, the vessels on the surface of the brain were found to be congested but there was no evidence of meningitis apart from this.
The cavernous sinus was opened and found to contain blood clot and pus.
Examination of pus showed the causative organism to be the haemolytic streptococcus.

Web Formation and Demonstration of the Tubercle Bacillus.

Each specimen of cerebro spinal fluid was allowed to stand undisturbed for a period of twelve to twenty-four hours, at the end of which time it was examined for web formation.

The formation of a web is due to excess fibrin being present in the fluid and is therefore never found in normal fluids.

A delicate web suspended from the surface of the fluid is characteristic of tuberculous meningitis and this was found to be present in 100% of cases in the series. A web was not observed at any time in normal fluids or in the fluids from cases of meningismus, lymphocytic meningitis, encephalitis or poliomyelitis.

A coarse type of web was sometimes observed in the slightly turbid fluids of cerebro spinal fever and in brain abscess.

Clark found web formation a constant feature of tuberculous meningitis and considers it of considerable diagnostic importance. He records one case which had the features of a tuberculous meningitis but was not labelled such because of the absence of a web. The case turned out to be non-tuberculous as shown by a sterile fluid culture, a negative guinea pig test and the complete recovery of the patient.

The formation of the web in tuberculous meningitis fluids gives one the opportunity of demonstrating the presence of the tubercle bacillus which is irrefutable evidence of the nature of the disease. As the web forms, the tubercle bacilli become involved in the mesh. The web is transferred to a slide and teased out as much as possible. The slide is then stained by the Ziehl Neelsen method to demonstrate the tubercle bacillus and examined under the microscope.

There is great diversity of opinion among various observers as to the frequency with which the organism can be demonstrated by this method. In my series, I was able to demonstrate the tubercle bacillus in 73% of cases at the first lumbar puncture, and in 80% of

cases after repeated lumbar puncture.

Clark states that he was able to demonstrate the organism in only 50% of his cases but he adopted the method of centrifuging the specimen and examining the deposit. This, in my experience, was less reliable than examining the web for organisms.

Stewart, in his investigations, employed both lumbar puncture and cisternal puncture on each of his patients. Both specimens were examined by the two methods, i.e., by centrifuging the specimen and by allowing a web to form. His results are very interesting in that they show that by lumber puncture only 57% of cases were positive, whereas by cisternal puncture 100% positive results were obtained.

Ingham was able to demonstrate the tubercle bacillus in 82 out of 84 cases but he points out that in many cases, prolonged search was necessary. The length of time spent in searching varied from 2 minutes to 2¼ hours; the average was from 25 to 30 minutes.

Hemenway after prolonged search claimed success in 100% of cases investigated.

It appears therefore that the percentage of positive results obtained depends on the length of time one is willing to spend in searching.

From my experience I would state that the main points to be observed in order to demonstrate the organism successfully are

1. To have as much fluid as possible - 10 cc. or more if it is available - in order that a fair sized web may form.

2. The web must be removed carefully from the fluid to the slide and teased out as much as possible.

3. Prolonged search may frequently be necessary. On several occasions only one tubercle bacillus was observed in the entire web.

Protein Content of the Cerebro Spinal Fluid.

The protein content of the C.S.F. was estimated both qualitatively and quantitatively. Three qualitative tests were investigated:-

1. The Pandy Test.
2. The Salicyl Sulphonic Acid Test.
3. The Tannic Acid Test.

Pandy Test.

To 1 cc. of a saturated aqueous solution of carbolic acid in a test tube, one or two drops of C.S.F. are added. If protein is present in excess, a white precipitate forms as the C.S.F. enters the carbolic acid and if shaken up, the contents of the tube become turbid.

Salicyl Sulphonic Acid Test.

To 1 cc. of C.S.F. in a test tube, one drop of 2% salicyl sulphonic acid is added and a white precipitate is formed when excess of protein is present.

Tannic Acid Test.

A small quantity of 5% tannic acid is placed in a watch glass and 1 drop of C.S.F. is added. In the presence of excess protein a precipitate is formed which reaches its maximum within a minute, after which it remains stationary.

The Tannic Acid Test was first described by Newman and in my experience has certain advantages over the other methods.

1. A 5% solution of tannic acid is easily prepared.
2. The white precipitate shows up very clearly against the brown colour of the tannic acid and from this point of view makes the test more satisfactory by being more sensitive than the others.

One disadvantage of tannic acid is that a fungus appears in the solution within the course of a few days

after it is made up and this spoils to some extent the delicate nature of the test. This can be overcome by filtering the tannic acid once per week but I have found a more convenient method is to add a small amount of carbolic acid to the tannic acid, thus preventing the growth of the fungus and it does not interfere in any way with the accuracy of the test.

One advantage that both the Pandy Test and the Tannic Acid Test have over Salicyl Sulphonic Test is that only one or two drops of C.S.F. are required as against 1 cc. in the latter method. This is rather important when a large number of investigations are being carried out on a sample of C.S.F. which is frequently limited in amount especially if obtained from a young child.

After investigation of the three methods of estimating protein described above, the Tannic Acid method was selected for convenience and used as a routine. Actually the precipitate obtained by this method is due to globulin but as the globulin is usually present in a fixed proportion to the total amount of protein, any increase in globulin indicates an increase of total protein.

Quantitative Tests.

I consider all the information that is necessary about the protein content of the C.S.F. can be obtained from a simple qualitative test. The total protein content was estimated quantitatively however, in order that the above statement could be substantiated by figures and so make the work complete from a scientific standpoint.

Two quantitative tests were investigated:-

1. Nitric Acid Method.
2. Trichlor-acetic Acid Method.

Nitric Acid Method.

Into a series of six small tubes 0.5 cc. of distilled water is measured. Into the first tube 0.5 cc. of C.S.F. is measured and mixed thoroughly.

Remove 0.5 cc. and place in a second tube, mix thoroughly and transfer 0.5 cc. to the third tube. This is continued down the series of tubes to the last one from which 0.5 cc. is removed and discarded. A tube is placed at the beginning of the row containing only 0.5 cc. of C.S.F. Seven similar tubes, each containing 1.0 cc. of concentrated nitric acid are placed parallel to the first set of tubes. The varying dilutions of the C.S.F. are then transferred to the second series of tubes by means of a pipette and layering them on the nitric acid with care. After two minutes the tube is noted in which the white ring, which develops, is just visible. The amount of protein present is obtained by multiplying the dilution value of the tube by 0.0033.

The results are given directly in the following table:-

Tube Number	Dilution Value	Protein (Gms) per 100 cc
1	1	0.0033
2	2	0.0066
3	4	0.0132
4	8	0.0264
5	16	0.0528
6	32	o.1056
7	64	0.2112

The method described above was used extensively to begin with in the investigation until it was found that the Trichlor-Acetic Acid method was much quicker to perform and just as accurate for the purposes of this investigation.

Trichlor-acetic Acid Method.

This is carried out by means of the proteinometer and a suitable instrument of this kind is manufactured by Baird and Tatlock (Son) Ltd. The method is as follows:-

A small amount of the C.S.F. for examination is poured into a watch glass. 1 cc. of this fluid is

taken by means of a pipette and placed in a suitable test tube and to this is added, by means of a second pipette, 0.1 cc. of 25% trichlor-acetic acid. The mixture is allowed to stand for 2 minutes, and the resulting turbidity is compared with specially prepared standard turbidity tubes. If the resulting turbidity is outside the range of the standards, the mixture should be diluted 1 in 5 (or in exceptional cases, 1 in 10) with physiological saline. The numbers on the standard tubes represent milligrammes of protein per 100 cc. if the fluid has not been diluted. If the fluid is diluted multiply by 5 or 10 as the case may be.

In practice the time taken to estimate the protein content by means of the proteinometer is not much longer than the time for the simple qualitative method and by reason of the greater accuracy of the former method it is much to be preferred when the necessary equipment is available.

By the qualitative method, after some experience, the extent of the increase in the protein was classified as slight, moderate or marked.

In tuberculous meningitis the protein increase was either moderate or marked in every case but never at any time was it classified as a slight increase. (See Page 57 Table IXa)

Meningismus showed no increase of protein.

Lymphocytic meningitis was never noted to show more than a slight increase of protein. This is an important diagnostic point because the cell count and type of cell in both tuberculous meningitis and lymphocytic meningitis fall within the same category and the first indication that a case is not tuberculous meningitis but lymphocytic meningitis may be had from an estimation of the protein content. (See Page 58 Table IXb)

Cases of poliomyelitis usually showed only a slight increase of protein. (See Page 58 Table IXc)

Fluids showing xanthochromia all gave a marked increase of protein due to the presence of the blood plasma

proteins in the cerebro spinal fluid.

In brain abscess the protein content of the C.S.F. varied considerably.

Table IXa - Estimation of Protein.

Tuberculous Meningitis

Case Number	Qualitative Estimation.	Quantitative Estimation.
1	++	
2	+++	
3	++	
4	++	
5	++	
6	+++	
7	++	
8	+++	
9	+++	
10	++	
11	++	
12	+++	
13	++	
14	++	
15	+++	
16	++	
17	+++	
18	+++	
19	+++	
20	+++	
21	++++	* 3379 mgm
22	++	52 "
23	++	52 "
24	+++	211 "
25	+++	211 "
26	++	52 "
27	+++	211 "
28	++	52 "
29	+++	105 "
30	+++	105 "
31	+++	* 211 "
32	++	52 "
33	+++	* 211 "
34	++	52 "
35	++	60 "

(Continued overleaf)

Table IXa Continued

Case Number	Qualitative Estimation.	Quantitative Estimation.
36	++	52 mgm
37	++	60 "
38	++	80 "
39	++	70 "
40	++	50 "
41	+++	* 150 "
42	+++	90 "

Table IXb - Lymphocytic Meningitis.

Case Number	Qualitative Estimation.	Quantitative Estimation.
1	+	
2	+	
3	+	
4	+	
5	+	
6	+	
7	+	30 mgm
8	+	26 "
9	normal	20 "
10	+	40 "

Table IXc - Poliomyelitis.

Case Number	Qualitative Estimation.	Quantitative Estimation.
1	*	
2	+	
3	+	
4	+	
5	++	
6	+	30 mgm
7	normal	2o "
8	++	50 "
9	+	40 "

* Case 21 - Marked xanthochromia
* Cases 31, 33 and 41 - Slight xanthochromia.

Quantitative Estimation of Protein.

The normal value for the protein content of the C.S.F. has been variously stated by different observers.

Stewart and Dunlop (Clinical Chemistry in Practical Medicine) ..... 14 - 50 mgm.
Harrison (Chemical Methods in Clinical Medicine) ..... 10 - 35 mgm.
Greenfield (The Interpretation of Reports on the C.S.F.) ..... 20 - 35 mgm.

By the methods I adopted to estimate the protein I found that normal fluids never gave a figure above 25 mgm. Tuberculous meningitis cases gave a figure which was never below 50mgm (the minimum reading being 53 mgm and the maximum 422 mgm) When xanthochromia was present in tuberculous meningitis fluids the protein content was much higher, e.g., in Case No. 21 where there was a content of 3379 mgm per 100 cc. In poliomyelitis the protein varied from 20 to 50 mgm.

Most observers are agreed that the protein content is always increased in tuberculous meningitis.

Clark states that the protein was found to be increased in all his cases of tuberculous meningitis. His test for protein was qualitative so that no figures are available of the range within which the increase lies and the number of cases examined is not stated.

Stewart investigated the protein content of 30 cases of tuberculous meningitis and found that 25 cases showed a definite increase, the figure varying from 70 to 400 mgm. According to Stewart 5 cases were within normal limits and gave the following values:- 57, 48, 35, 30 and 45 mgm.

I have not observed cases of tuberculous meningitis in my series with a protein content below 50 mgm, but on several occasions when cases of miliary tuberculosis with no meningeal symptoms were lumbar punctured the cerebro spinal fluid showed a protein content which was increases above the normal limits but did not exceed 50 mgm. These cases, however, did not

show definite clinical signs of meningeal involvement and at post mortem the typical appearance of tuberculous meningitis was absent.

Stewart, in discussing his findings, accepts the normal value of protein in the cerebro spinal fluid as being from 15 to 55 mgm.

My observations suggest that the upper limit is too high and I consider the normal protein content to be between 10 and 25 mgm. This approximates to Harrison's view that the protein content of normal fluid is between 10 and 35 mgm. Giustra, in a series of 10 cases of tuberculous meningitis found that the protein content varies from 43 to 175 mgm. In poliomyelitis the protein content of his cases varied from 30 to 38 mgm, which corresponds to a slight increase above normal by my standards and corresponds also with my findings of the protein content in this condition.

Sugar Content of the Cerebro Spinal Fluid.

Estimation of the sugar content of the cerebro spinal fluid was carried out to ascertain if it was of any assistance in the diagnosis of tuberculous meningitis. The quantity of sugar present was estimated both qualitatively and quantitatively.

Qualitative Method.

To 1 cc. of fluid in a test tube, 0.25 of Fehling's Solution is added and the mixture boiled. If sugar is present, the Fehling's solution is reduced and the degree of reduction can be estimated by the resulting colour.
In normal fluids the colour after boiling is brown or reddish-brown. If allowed to stand, a brown or brick-red deposit froms and the supernatant fluid is pale blue in colour.
If the sugar content is diminished only slight reduction takes place and if allowed to stand, only a slight deposit results and the supernatant fluid remains purple.
If no sugar is present or if it is present in very small amounts, the colour of the fluid remains unaltered and there is no deposit.
In the presence of excess of sugar a yellow colour develops.

In tuberculous meningitis there is a definite diminution of the sugar content practically in every case. In this series of 41 cases, 20 specimens showed no reduction of Fehling's solution and 20 others produced a slight reduction. In 1 case only was the reduction of Fehling's solution within the limits of normal. (See case 5, table 10.)

Table X - Sugar Content as Estimated by Qualitative Method.

Case No.	Sugar	Case No.	Sugar
1	Absent	21	Absent
2	Absent	22	Trace
3	Absent	23	Trace
4	Diminished	24	Diminished
5	Sl. Dimin.	25	Absent
6	Diminished	26	Trace
7	Diminished	27	Trace
8	Absent	28	Absent
9	Absent	29	Absent
10	Absent	30	Trace
11	Absent	31	Diminished
12	Diminished	32	Trace
13	Diminished	33	Absent
14	Trace	34	Absent
15	Absent	35	Diminished
16	Absent	36	Absent
17	Trace	37	Trace
18	Absent	38	Absent
19	Trace	39	Absent
20	Trace	40	Absent
		41	Trace

Quantitative Method.

In order to estimate quantitatively the amount of sugar present the method of Folin and Wu was adopted.

Method of Folin and Wu.

Principle:- The proteins are precipitated by tungstic acid and removed by filtration. The protein-free filtrate is heated with an alkaline cupric tartrate solution under standard conditions. The cupric tartrate is altered to the cuprous salt by the sugar present. It is then treated with phosphomolybdic acid which is reduced in proportion to the amount of cuprous salt and therefore in proportion

to the quantity of sugar. The compound formed by the reduction of phosphomolybdic acid is blue, and the intensity of this colour is compared in a calorimeter with that of a standard solution of pure dextrose similarly treated.

Solutions.

1. 10% sodium tungstate ($Na_2WO_4 \cdot 2H_2O$).
2. 2/3 normal sulphuric acid.
3. Alkaline copper solution.

Dissolve 40 gms. anhydrous sodium carbonate in about 400 cc. of water and transfer to a 1,000 cc. flask. Add 7.5 gm. of tartaric acid and wait till this has dissolved. Then transfer quantitatively to the flask 4.5 gm. of crystalline copper sulphate which has been dissolved in about 100 cc. of water. Mix and make up to volume. A sediment often forms in time, in which case decant the clear supernatant solution.

4. Phospho-molybdic acid solution.

Dissolve 35 gms. of molybdic acid and 5 gms. of sodium tungstate in 200cc of 10% NaOH plus 200 cc. of water in a litre beaker. Boil vigorously for 20 to 40 minutes so as to remove as completely as possible the ammonia present in the molybdic acid. Cool and transfer to a 500 cc. volumetric flask, washing in with sufficientwater to make the volume about 350 cc. Add 125 cc. of 89% w/w phosphoric acid (S.G. 1.75) and make up to the 500 cc.

5. Stock glucose solution. (1%).

Prepare a saturated solution of benzoic acid by adding 2.5 gm. to 1,000 cc. of boiling water, and allow to cool. Dissolve 1 gm. of pure dry glucose in 100 cc. of the saturated benzoic acid. This solution appears to keep indefinitely.

6. Glucose standard solutions (0.01 and 0.02 %).

These are prepared by diluting the stock 1% solution 1 in 100 and 2 in 100 respectively with the saturated benzoic acid.

Technique.

Precipitate the proteins as follows:-
1 cc. C.S.F.
8.5 cc. water
0.25 cc. sod. tungstate
0.25 cc. 2/3 N H_2SO_4
Mix and stand till the precipitate clumps.
Filter through an acid-washed filter paper (Whatman No. 41).
In a Folin's tube place 2 cc. of filtrate and 2 cc. of alkaline copper solution.

To prepare standard A, place 2 cc. of 0.01% glucose and 2 cc. of alkaline copper solution in a Folin's tube.

To prepare standard B, place 2 cc. of 0.02% glucose and 2 cc. of alkaline copper solution in a third Folin's tube.

Mix the contents of each Folin's tube and place in a boiling water bath for exactly six minutes. Cool for one or two minutes only, and without shaking (to avoid re-oxidation of cuprous oxide by air) add to each tube 2 cc. of phosphomolybdic acid solution. When the cuprous oxide has dissolved, dilute to the 25 cc. mark with water and mix thoroughly. Compare the unknown, in a calorimeter, with the standard A or B, whichever it most nearly matches in colour.

Calculation. (Standard A).

Let S be the reading of the standard.
Let U be the reading of the unknown.
Let X be mgm. of glucose in the 1 cc. of C.S.F. used.
The standard tube contains 2 cc. of 0.01% glucose.
100 cc. of standard A solution contains 10 mgm. of glucose.
∴ 1 cc. " " " " " $\frac{10}{100}$ "
∴ 2 cc. " " " " " $\frac{20}{100}$ = 0.2 mgm.
$X \times U = 0.2 \times S$.
∴ $X = \frac{0.2 \times S}{U}$ Mgm. of glucose.
10 cc. of C.S.F. filtrate are derived from 1cc of C.S.F.
∴ 2 cc. " " " " " 0.2cc. "
∴ 0.2 cc. of C.S.F. contains $\frac{0.2 \times S}{U}$ mgm. of glucose.
∴ 1 cc. " " " $\frac{0.2 \times S}{U \times 0.2}$ " " "
∴ 100 cc. " " " S/U x 100

Using B standard.

C.S.F. sugar equals S/U x 200 mgm. per 100 cc.

The normal sugar content of the cerebro spinal fluid has been variously stated by different observers.

Harrison (Chemical Methods in Clinical Medicine) 45 to 100 mgm.
Stewart and Dunlop (Clinical Chemistry in Practical Medicine) 60 to 90 mgm.
Greenfield (Interpretations of reports on C.S.F.) 50 to 75 mgm.

In my experience I have observed variations in the normal sugar content from 43 mgm. to 100 mgm. per 100 cc. In tuberculous meningitis the sugar content appears to be always below this normal range. The limits of sugar content observed in a short series of cases of tuberculous meningitis were a minimum of 6.7 mgm. and a maximum of 29 mgm, per 100 cc.

See Table Xl underneath.

Table Xl - Quantitative Estimation of Sugar in Tuberculous Meningitis.

Case No.	Sugar Content in mgm. per 100 cc.
25	6.7
26	28
27	29
28	14
29	20
30	19
31	22

The quantitative method of sugar estimation is a time taking procedure and for ordinary side-room testing the qualitative estimation is quite sufficient for all practical purposes.

In tuberculous meningitis the sugar content has been shown to be diminished or absent. (See Tables X and Xl.)
The cerebro spinal fluid sugar in meningismus was normal in amount.
In lymphocytic meningitis the sugar was either normal or only slightly diminished, In one case only was there a slight increase of sugar. (See table Xlla).

Table Xlla. - Lymphocytic Meningitis.

Case No.	Sugar Content
1	Sl. Diminished
2	Normal
3	Normal
4	Sl. Diminished
5	Diminished
6	Normal
7	Normal
8	Normal
9	Normal
10	Sl. Increased

In cases of cerebro spinal fever where the fluid was clear or only slightly turbid, such as is seen in cases clearing up without treatment, the sugar content was variable. The sugar was frequently found to be diminished at first, but as the condition improved, it rose, and in a few cases it was observed to be actually increased above normal.
In xanthochromic fluids due to subarachnoid haemorrage the sugar was found to be normal and this was proved to be of importance in differentiating this condition from tuberculous meningitis where the fluid had developed a xanthochromic staining.
Brain abscess cases showed either a normal or diminished sugar content of the cerebro spinal fluid.

(See table Xllb.)

Table XIIb. - Brain Abscess.

Case No.	Sugar Content.
1	Normal
2	Diminished
3	Trace
4	Normal

In cases of poliomyelitis and polioencephalitis the sugar was found to be normal or slightly increased in amount. (See table XIIc.)

Table XIIc. - Poliomyelitis.

Case No.	Sugar Content.
1	Normal
2	Normal
3	Increased
4	Sl. Increased
5	Sl. Increased
6	Normal
7	Normal
8	Sl. Increased
9	Normal

Where there is increased intracranial pressure apart from an infective condition of the meninges the cerebro spinal fluid sugar content is frequently found to be increased above normal.

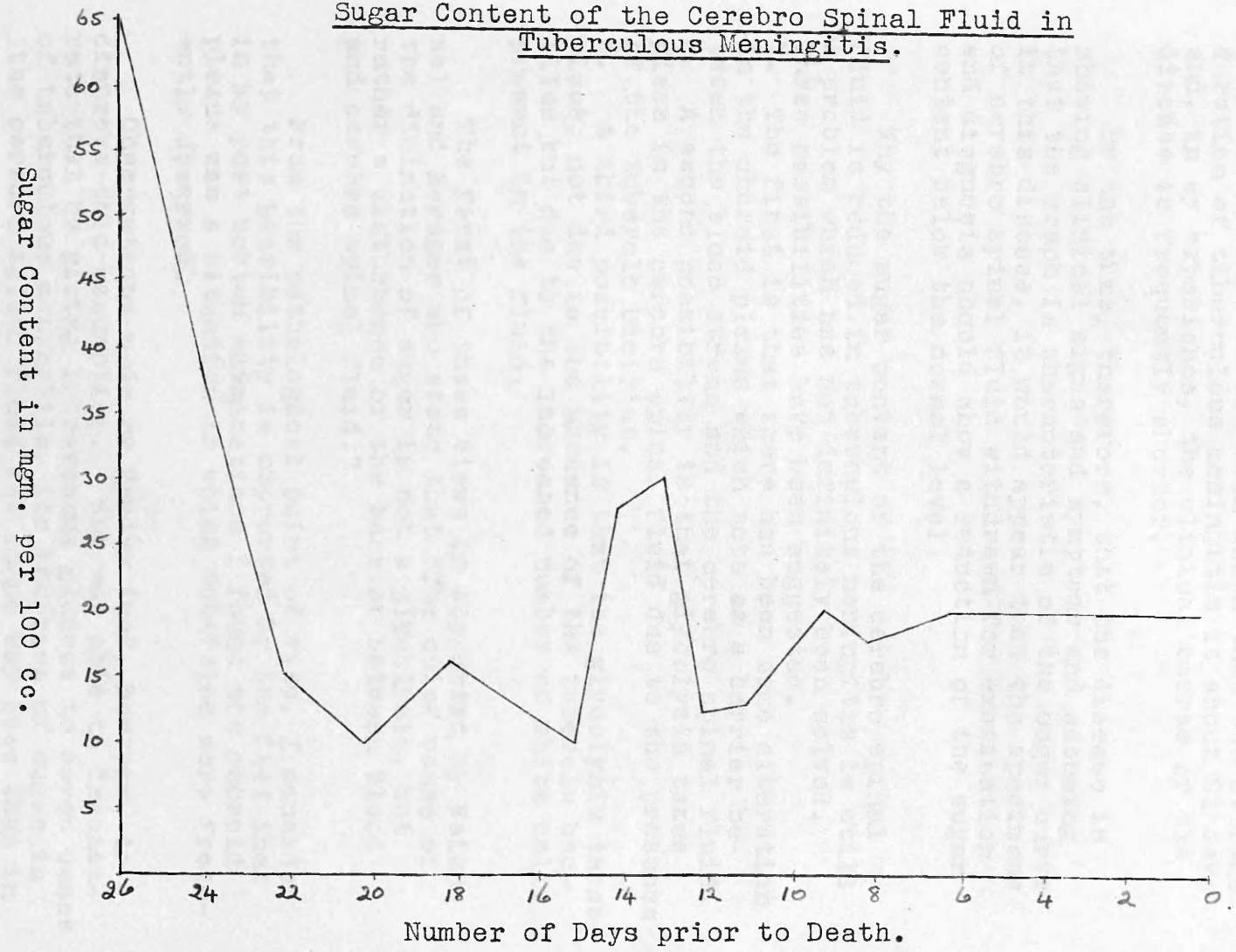
From my observations, I would state that if the sugar content of the cerebro spinal fluid is not diminished, the case is unlikely to be tuberculous meningitis. This view is, however, not a general one. Clark states that in tuberculous meningitis, the sugar content is diminished.
Stewart, in his series of cases observed that the

sugar content was diminished in the majority but he actually observed a few in which the sugar was increased. He records one case where the sugar content amounted to 125 mgm. per 100 cc.
Giustra observed in his series of 10 cases that the sugar content varied from 10 to 77 mgm. per 100 cc.
The problem of the sugar content in tuberculous meningitis was investigated very thoroughly by Weichsel and Herzger and these workers have produced a graph which, in their opinion, is characteristic of the variations in the sugar content of the fluid during the course of the illness.
The time factor is stated as "The number of days before death".
The sugar is recorded in mgm. per 100 cc. of cerebro spinal fluid. (See table XIII).

Table XIII.

Day Prior to Death	Sugar Content mgm. per 100 cc.	Day Prior to Death	Sugar Content mgm. per 100 cc.
26th	65	13th	30
24th	38	12th	12
22nd	15	11th	13
20th	10	9th	20
18th	16	8th	18
15th	10	6-0	20
14th	28		

See next page for corresponding graph.


Sugar Content of the Cerebro Spinal Fluid in Tuberculous Meningitis.
Sugar Content in mgm. per 100 cc.
65
60
55
50
45
40
35
30
25
20
15
10
5
26
24
22
20
18
16
14
12
10
8
6
4
2
0.
Number of Days prior to Death.

It will be seen from this graph that the sugar content falls to a level below normal about the 24th day prior to death.

Clinically, it has been shown that the average duration of tuberculous meningitis is about 21 days and, in my experience, the clinical course of the disease is frequently shorter.

By the time, therefore, that the disease is showing clinical signs and symptoms and assuming that the graph is characteristic of the sugar curve in this disease, it would appear that the specimens of cerebro spinal fluid withdrawn for examination and diagnosis should show a reduction of the sugar content below the normal level.

Why the sugar content of the cerebro spinal fluid is reduced in tuberculous meningitis is still a problem which has not definitely been solved. Three possibilities have been suggested.
1. The first is that there has been some alteration in the choroid plexus which acts as a barrier between the blood stream and the cerebro spinal fluid.
2. A second possibility is that glycolysis takes place in the cerebro spinal fluid due to the presence of the tubercle bacillus.
3. A third possibility is that the glycolysis takes place, not due to the presence of the tubercle bacillus but due to the increased number of white cells present in the fluid.

The first of these views is supported by Weichsel and Herzger who state that "The chief cause of the diminution of sugar is not a glycolysis, but rather a disturbance of the barrier between blood and cerebro spinal fluid."

From the pathological point of view, I consider that this possibility is supported by the fact that in my post mortem examinations I found the choroid plexus was a situation in which tubercles were frequently observed.

Observations made by Hendry tend, however, to disprove this assumption. She was able to demonstrate that by giving intravenous glucose to seven cases of tuberculous meningitis, the increase of sugar in the cerebro spinal fluid was in no way less than in

a small number of non-meningitic controls. From this she concluded that the diminished sugar was not due to an alteration in the blood-brain barrier. In support of this theory she was able to show a rise of the lactic acid content simultaneous with a reduction of sugar.

To investigate whether the presence of organisms in the cerebro spinal fluid was capable of causing glycolysis, Hendry incubated normal sterile cerebro spinal fluid with cultures of various bacteria (staphylococcus albus and aureus, meningoccus, pneumococcus, bacterium coli and the tubercle bacillus). Only in the case of bacterium coli was the sugar content of the fluid much reduced.

Normal sterile cerebro spinal fluid was also incubated with sterile emulsions of polymorphonuclear leucocytes and lymphocytes. In the case of the polymorphs, the sugar content was reduced but the lymphocytes had no glycolytic properties.

It would appear then, from these experiments, that in tuberculous meningitis, neither the presence of the tubercle bacillus nor the presence of the lymphocytes in the cerebro spinal fluid are capable of causing a reduction of the sugar content.

Estimation of Chlorides in Cerebro Spinal Fluid.

This is done by titration with a standard Silver Nitrate Solution. The solution is prepared by weighing accurately 2.906 gm. of pure silver nitrate and dissolving the salt in 500 cc. of distilled water.

1 cc. of this solution = 2 mgm of sodium chloride.

Technique.

Into a 50 cc. flask deliver 15 cc. of distilled water and add 2 cc. of C.S.F. Three drops of 10% potassium chromate are added and the contents of the flask are titrated against the standard silver nitrate solution until the yellow colour changes to an orange tint - normally this requires from 7 to 7.5 cc. of silver nitrate.

In dealing with highly albuminous fluids, remove the protein by taking 2.5 cc. of C.S.F. and shake with 7.5 cc. of absolute alcohol. Centrifugalise and collect 8 cc. of supernatant fluid. This is equivalent to 2 cc. of C.S.F. Titrate as before. Each cubic centimetre of standard silver nitrate indicates 100 mgm of chloride expressed as sodium chloride.

$$\underset{169.9}{Ag.NO_3} + \underset{58.46}{Na.Cl} = Na.NO_3 + Ag.Cl.$$

$\therefore$ 169.9 gm $Ag.NO_3$ is equivalent to 58.46 gm Na.Cl.

$$2.906 \text{ gm } Ag.NO_3 = \frac{2.906}{169.9} \times 58.46 = 1.0 \text{ gm Na.Cl.}$$

Thus 500 cc. of standard silver nitrate solution is equivalent to 1.0 gm Na.Cl. and 1 cc. = 1.0/500 which equals 2 mgm Na.Cl.

Two cc. of C.S.F. are used for the test and the number of cc. of standard silver solution in the titration multiplied by 50 and by 2 gives the chloride content in mgm Na.Cl.

The silver solution can be tested periodically against an accurately prepared saline solution (0.85% sodium chloride)

Most authorities are agreed that the normal amount of chloride in the cerebro spinal fluid lies between 700 and 760 mgm per 100 cc.

Ingham (British Medical Journal - 1937) ... 700 - 740 mgm
Stewart and Dunlop (Clinical Chemistry in Practical Medicine) .....Adults. 720 - 750 "
...Children. 700 - 760 "
Greenwood (Lancet - 1928) ..... 720 - 750 "
Harrison (Chemical Methods in Clinical Medicine) ..... 700 - 760 "

My experience has been that normal fluids have a chloride content of from 700 to 760 mgm per 100 cc.

In certain diseases, however, a reduction of chloride was observed when the C.S.F. was normal in all other respects. This included such diseases as pneumonia, gastro-enteritis, influenza and whooping cough with severe vomiting.

Table XIV.

Case No.	Chloride Content	Nature of Disease
59	650 mgm	Pneumonia
60	680 "	Broncho pneumonia
62	690 "	Enteritis
67	660 "	Influenze
90	660 "	Lobar pneumonia
112	670 "	Whooping cough with vomiting

In tuberculous meningitis the chlorides are diminished except very early in the disease. In three cases only did the chloride content fall within the limits of normality. The vast majority of cases were found to lie within the range of 600 to 680 mgm per 100 cc. and the lowest recorded value was 580 mgm per 100 cc. (See Page 74 Table XV.)

Table XV - Chlorides in the Cerebro Spinal Fluid of Tuberculous Meningitis.

Case Number	Chloride Content mgm. per 100 cc.	Case Number	Chloride Content mgm. per 100 cc.
1	620	22	650
2	660	23	650
3	620	24	640
4	660	25	640
5	690	26	620
6	630	27	660
7	720	28	600
8	700	29	600
9	660	30	640
10	650	31	580
11	670	32	660
12	710	33	660
13	680	34	600
14	650	35	610
15	630	36	630
16	580	37	620
17	630	38	600
18	680	39	620
19	670	40	660
20	600	41	600
21	610	42	630

A low chloride content in a clear or slightly turbid fluid together with a moderate or marked increase of protein is almost diagnostic of tuberculous meningitis, provided that the cells are chiefly lymphocytic.

The only exception was seen in cases of cerebro spinal fever which were clearing up and in these the chloride content was still low but these could be differentiated by the high percentage of polymorphs in the white cell count. One case only could not be differentiated by this method; this was a case of posterior basic meningitis. (See Page 99).

In lymphocyitc meningitis the chloride content was observed to fall within the limits of 680 to 770 mgm per 100 cc. (See Table XVI)

Table XVI - Chloride Content in Lymphocytic Meningitis

Case Number	Chloride Content mgm. per 100 cc.	Case Number	Chloride Content mgm. per 100 cc.
1	770	6	700
2	740	7	720
3	720	8	720
4	730	9	700
5	730	10	680

In xanthochromic fluids due to subarachnoid haemorrhage the chlorides were found to be normal (Table XVII)

Table XVII - Chloride Content in Xanthochromic Fluids (Non-tuberculous)

Case Number	Chloride Content mgm. per 100 cc.
1	760
2	780
3	710
4	690
5	750

In brain abscess the chlorides were usually found to be normal or diminished. (Table XVIII)

Table XVIII - Chloride Content in Brain Abscess.

Case Number	Chloride Content mgm. per 100 cc.
1	660
2	690
3	740
4	650

Increase of the chlorides appeared to be related to an increased intracranial pressure. One case of tuberculoma had a chloride figure as high as 820 mgm.

In poliomyelitis the chlorides were found to be normal or only slightly diminished. (Table XIV)

Table XIV - Chloride Content in Poliomyelitis.

Case Number	Chloride Content mgm. per 100 cc.	Case Number	Chloride Content mgm. per 100 cc.
1	710	6	670
2	770	7	700
3	780	8	690
4	720	9	700
5	710		

The reason for a drop in the chloride content of the cerebro spinal fluid is not altogether clear.

1. It may be due to repeated and severe vomiting. This was seen in certain cases of gastro enteritis and whooping cough. In tuberculous meningitis however, vomiting is not a feature of the disease after the first few days.

2. Inflammation involving the choroid plexus, may, to some extent, prevent the passage of chlorides from the blood to the cerebro spinal fluid and since this process is operative over a relatively long period in tuberculous meningitis this would explain the low values reached by the chlorides in this disease.

Ingham investigated the chloride content of the cerebro spinal fluid in 84 cases of tuberculous meningitis and in two cases only did the amount exceed 550 mgm. per 100 cc. The range of the remaining cases was from 420 to 550 mgm. The average chloride content of his cases was 510 mgm. per 100 cc.

I have not been able to demonstrate such low values and in my series the average chloride content was 640 mgm. per 100 cc.

Kinnear estimated the chloride content of a large series of cases of tuberculous meningitis on admission to hospital and found the average to be 675 mgm per 100 cc.

Stewart considers that the estimation of chlorides is of no value in the diagnosis of tuberculous meningitis. I have found, however, that it is certainly of some value. The fact that the chlorides are diminished is always a point in support of the diagnosis If a fluid which is clear or slightly turbid has a moderate increase of protein, an increases cell count with a high percentage of lymphocytes and a low chloride content then it is almost certainly a case of tuberculous meningitis - the only exception would possibly be an advanced case of posterior basic meningitis.

Giustra, in a series of 10 cases of tuberculous meningitis found that the chloride content ranged from 540 to 660 mgm. per 100 c.c.

Incertain cases, however, the chloride content is not much below the limits of normality and in such cases no value can be placed on this line of investigation. For example, a case of tuberculous meningitis with a chloride content of 680 mgm per 100 cc; although this figure is below the normal level the reduction is not sufficient to be significant and consequently has to be discounted.

Tryptophan and Levinson Tests.

From time to time special tests have been announced which have been claimed to be specific for tuberculous meningitis. Two tests appeared to me to merit this claim. These were the Tryptophan Test and the Levinson Test.

Tryptophan Test.

Method:

Place 15cc. of concentrated hydrochloric acid in a test tube and add 2 to 3 cc. of cerebro spinal fluid. To this is added two drops of a 2% solution of formaldehyde which should be prepared each time from 40% formaldehyde by making a 1 in 20 dilution. The mixture is shaken and allowed to stand for 4 to 5 minutes and then layered with 2 cc. of a 0.06% solution of sodium nitrite.

Interpretation of Results.

If a delicate violet ring appears at the junction of the fluids then the reaction is positive.

If the cerebro spinal fluid is purulent or xanthochromic the ring at the junction of the fluids is deep purple in colour and this is considered to be a pseudo-positive result.

If a brown ring appears, such as is seen at times in blood stained fluids, this is considered to be a negative result.

This test was carried out on a large number of fluids with the following results.

In tuberculous meningitis the characteristic violet ring was obtained in all cases except where the disease was complicated by the presence of xanthochromic staining in the fluid. This occurred in 4 cases and in two of these the ring was deep purple in colour.

In normal fluids no colour reaction was observed.

In two cases of lymphocytic meningitis characteristic positive results were obtained. In 4 other cases the violet ring obtained was more faint than the typical reaction seen in tuberculous meningitis but since it was impossible to distinguish between the finer degrees of colour variation it was necessary to consider these as faint positive results.

Fluids obtained from cases of poliomyelitis gave the following results:- no cases gave the characteristic positive reaction but four cases gave faint positive reactions

In brain abscess when the fluid was turbid the result was pseudo-positive. Two cases were examined however, in which the fluid was quite clear and in one of these a characteristic positive result was obtained. A characteristic positive reaction was also obtained in a case of subdural abscess, and in the only case of posterior basic meningitis.

Several fluids showing xanthochromia as a result of subarachnoid haemorrhage were examined. When the xanthochromia was marked in degree the resulting ring was deep purple and therefore psuedo-positive. In three cases where the xanthochromia was slight the test gave a typical positive reaction.

With purulent fluids in cerebro spinal fever the result was always pseudo-positive. In four cases, however, where the fluid was only slightly turbid due to a mild attack which was clearing up without treatment, characteristic positive results were obtained.

The only other occasions on which typical positive results were obtained were in fluids which were non-tuberculous; one was a case of encephalitis and one was a case of tuberculoma.

In a large series of specimens of cerebro spinal fluids negative results were obtained and these were drawn from a wide variety of conditions which because of some feature or other led one to suspect tuberculous meningitis as a possible diagnosis. Such conditions included tonsillitis, otitis media, pneumonia, enteritis, bronchitis, influenza, myocitic, tuberculous

broncho-pneumonia, convulsions in infancy, epilepsy and septicaemia.

Spillane carried out the Tryptophan Test on a series of 172 cases. 29 of the fluids were purulent, haemorrhagic or xanthochromic and all gave false positive reactions. 32 of the fluids examined were from cases of tuberculous meningitis and in 30 of these the test was positive. The two negative fluids were otherwise typical of tuberculous meningitis.

The cerebro spinal fluid was examined from 25 cases of tuberculosis involving the chest, bones or joints, but showing no meningeal symptoms, and the test was negative in each case.

A series of 61 cases of disease of the central nervous system of a non-tuberculous nature was investigated. These consisted of such conditions as meningismus, cerebral abscess, cerebral tumour, disseminated sclerosis, general paralysis, tabes dorsalis, encephalitis, etc., and in each case the test was negative

A series of 25 normal cerebro spinal fluids were examined and all proved to be negative.

Spillane suggests that tryptophan, which produces the colour reaction in the test, is synthesised by tubercle bacillae in the cerebro spinal fluid.

Aiello found the Tryptophan Test to be positive in only 90% of cases of tuberculous meningitis and he found no true positive in any other condition. He states that a negative Tryptophan Test practically excludes the diagnosis of tuberculous meningitis.

Brugi obtained a positive reaction in 12 out of 12 cases of tuberculous meningitis and no true positive in 30 other conditions.

Schumacher records a positive reaction in 100% of a series of 32 cases of tuberculous meningitis and one positive reaction in a case of cerebral tumour.

Baxter states that in a series of 41 cases of

of tuberculous meningitis investigated by him, he obtained a positive tryptophan reaction in every case and in a series of 32 control cases only one gave a positive reaction, this being a case of cerebral tumour.

Lichtenberg in a series of 25 cases of tuberculous meningitis found them all positive and he states from his investigations that "all negative tryptophan fluids were from non-tuberculous lesions of the meninges"

Giustra, on the other hand, examined the cerebro spinal fluids of 10 cases of tuberculous meningitis and records that the tryptophan test was positive in only three out of the ten cases. He states also that he found the tryptophan test positive in 2 cases out of 25 non-tuberculous fluids, both fluids being purulent.

My findings agree with those of Aiello, Brugi, Schumacher, Baxter and Lichtenberg in that all cases of tuberculous meningitis show positive reactions to the tryptophan test. I have been able to show, however, that if the cerebro spinal fluid obtained from a case of tuberculous meningitis is xanthochromic due to haemorrhage from the congested vessels on the surface of the brain, then the test is no longer positive but gives a pseudo-positive result due to the marked excess of protein present.

Baxter found that one case in a control series of 32 cases gave a positive reaction. In my control series of at least 120 cases I have been able to show 15 cases in which a typical positive result was obtained in conditions other than tuberculous meningitis and in addition 10 other cases which were classified as slightly positive. (See Page 82 Table XX)

It is difficult to account for the widely divergent results obtained by Giustra except that on the assumption that some fault in his technique upset this part of his work. In regard to his observations on protein, sugar, chlorides and the cell content of the cerebro spinal fluid in various intracranial conditions which he has investigated, I find myself in much closer agreement.

Table XX - Cases other than Tuberculous meningitis showing a positive Tryptophan Test.

Disease	Case Number	Tryptophan Test
Brain Abscess	1	Typical positive
	3	Slight positive
Lymphocytic Meningitis	1	Slight positive
	2	Typical positive
	3	Typical positive
	4	Slight positive
	5	Slight positive
	7	Slight positive
Poliomyelitis	1	Slight positive
	2	Slight positive
	4	Slight positive
	5	Slight positive
Encephalitis	1	Typical positive
	3	Slight positive
Subarachnoid Haemorrhage with slight Xantho-chromia	1	Typical positive
	3	Typical positive
	4	Typical positive
Cerebro-spinal Fever (fluid only slightly turbid)	1	Typical positive
	2	Typical positive
	5	Typical positive
	6	Typical positive
Cerebral Haemorrhage	1	Typical positive
Tuberculoma	1	Typical positive
Posterior Basic Meningitis	1	Typical positive
Subdural Abscess	1	Typical positive

It would appear therefore from these investigations that the claim made for the Tryptophan Test being diagnostic of tuberculous meningitis cannot be upheld.

The test is certainly positive in all cases of tuberculous meningitis except those complicated by the presence of xanthochromic staining of the fluid, in which case the result is pseudo-positive. There are, however, a number of conditions which have been shown to give a characteristic positive result and

and which are not cases of tuberculous meningitis.

All that can be claimed for the test is that a positive result is suggestive of tuberculous meningitis but is by no means diagnostic of this condition. Secondly, it can be stated that if the reaction is negative the case is certainly not one of tuberculous meningitis.

Spillane suggests that tryptophan appears in the cerebro spinal fluid due to synthesis by the tubercle bacillus. Aiello considers that the reaction is due to free tryptoplan being separated from fibrin in the cerebro spinal fluid by the action of autolytic enzymes.

My opinion of the Tryptophan test is that it merely indicates the amount of protein present in the fluid. Tryptophan is said to be a breakdown product of protein and during my investigations I have noticed a definite co-relation between the amount of protein present in the fluid and the intensity of the colour reaction in the Tryptophan Test. When the protein is only slightly above normal, then the colour ring obtained is a faint violet and I classify this as a faint positive result. When the increase of protein is moderate in amount such as one sees in tuberculous meningitis then the characteristis delicate violet colour is obtained. When the protein is present in great excess as is seen in purulent fluids and xanthochromic fluids then the colour reaction is more intense and a purple ring is obtained.

The Levinson Test.

Method.

Into each of two test tubes, 8 mm. in diameter, 1 cc. of cerebro spinal fluid is measured. To one tube, 1 cc. of 2% mercuric chloride is added while to the other, 1 cc. of 3% sulphosalicylic acid is added. The tubes are stoppered, shaken and placed vertically in a rack where they are left at room temperature. After 22 hours the tubes are shaken and the readings of the height of the column of precipitate are made after 24 hours. They are checked again after 48 hours.

The precipitate in the sulphosalicylic acid tube will be seen to form almost immediately and is rather heavy and compact. In the mercuric chloride tube, light floccules form slowly and may adhere to the sides of the tube.

Interpretation of Results.

A positive test consists of a precipitate with mercuric chloride of 5 mm. or more in height and equal to at least twice the amount in the sulphosalicylic acid tube. Less than 5 mm. precipitate in the mercuric chloride solution has been considered a negative test.

A series of normal fluids was examined with negative results in every case. It was found that there was practically no precipitate or only very slight precipitate in either tube.

A series of 26 abnormal fluids were examined by this method.
These consisted of:-

17	Cases of	tuberculous meningitis.
2	" "	C.S.F. with only slight turbidity of the fluid.
2	" "	poliomyelitis.
1	Case "	subdural abscess.
1	" "	influenzal meningitis (before the fluid became turbid).
1	" "	post basic meningitis.
1	" "	subarachnoid haemorrhage (with only slight xanthocromia).
1	" "	cavernous sinus thrombosis.

16 cases of tuberculous meningitis out of a total of 17 gave a positive result. One of these 16 cases was negative at the end of 24 hours, due to the precipitate in the sulphosalicylic acid tube not having settled completely, but when it was seen again after a further 24 hours, it was found to be quite a typical positive.

The one case which was negative was a case of tuberculous meningitis in which the fluid had xanthochromic staining and besides the Levinson Test being negative, the Tryptophan Test gave a deep purple pseudo positive result.

In non-tuberculous cases the test was usually found to be negative except in 1 case of posterior basic meningitis and 2 cases of poliomyelitis.

It is interesting to note that several of the cases which were non-tuberculous in origin and gave a negative result to Levinson's Test, were found to give quite a typical positive result to the Tryptophan Test. (See table XXl).

Table XXl.

Disease	Tryptophan Test	Levinson Test
Subdural Abscess	+	-
Mild C.S.F.	+	-
Subarachnoid Haemorrhage	+	-
Mild C.S.F.	+	-

A series of purulent fluids was examined by the Levinson Test and all proved to be negative.

It would appear from these observations that the Levinson Test is positive in all cases of tuberculous meningitis except where there is xanthochromic staining of the fluid and in these instances the result appears to be upset by the presence of the plasma protein of the blood which has reached

the fluid as a result of haemorrhage into the sub-arachnoid space.

In certain cases where the Tryptophan Test has been positive, a negative Levinson Test has confirmed the condition to be non-tuberculous.

Neither the Levinson Test nor the Tryptophan Test was of value in differentiating the case of posterior basic meningitis from tuberculous meningitis.

The Levinson Test has not been carried out on such a large and varied series of cases as the Tryptophan Test and it would therefore be unwise to draw a comparison of their respective values, but superficially, it would appear that the Levinson Test is preferable, in that it gives on the whole, negative results in non-tuberculous meningitis cases when the Tryptoplan Test was positive.

Hurwitz, in his investigations, has shown that all cases of tuberculous meningitis give a positive Levinson Test and he states that a negative result rules out tuberculous meningitis. He found, however, that in a control series of 189 cases 25 positive results were obtained in cases other than tuberculous meningitis.

Messeloff showed that 6 cases of tuberculous meningitis all gave a positive reaction to the Levinson Test.

Giustra showed that in 10 cases of tuberculous meningitis, the Levinson Test was positive in all fluids and in a group of 24 control cases which were non-tuberculous, 4 positive results were obtained.

My findings are in agreement with each of the above, in that all cases of tuberculous meningitis gave a positive Levinson Test with the one proviso that, should the fluid have xanthocromic staining, the test will probably become negative. I have also shown that positive results can be obtained in cases which are not tuberculous meningitis.

All that can be claimed for the test, therefore, is that if the result is positive, then it is suggestive of tuberculous meningitis, but by no means diagnostic. Secondly, if the result is negative and provided the fluid had no xanthocromic staining, the case is certainly not one of tuberculous meningitis.

Differential Diagnosis based on the Examination of the Cerebro Spinal Fluid.

The characteristic features of the cerebro spinal fluid in tuberculous meningitis are as follows:-

1. The cell count is increased above normal limits - the figure lies most frequently between 4o and 500 cells per cu. mm.

2. The majority of the cells present are lymphocytes

3. If the fluid is allowed to stand, a characteristic web is formed.

4. The tubercle bacillus may be present in the fluid and if found is absolutely diagnostic in itself

5. The protein content is above normal - usually 50 mgm. or more per 100 cc. of fluid.

6. The sugar content is diminished.

7. The chloride content is diminished.

8. The Tryptophan Test is positive or if the fluid is xanthochromic it is pseudo-positive.

9. The Levinson Test is positive provided the fluid is not xanthochromic.

The conditions which are most likely to simulate tuberculous meningitis and which must be considered in a differential diagnosis when the fluid is examined are:-

1. Meningismus.
2. Septic Meningitis (meningococcal, pneumococcal etc.)
3. Acute Encephalitis.
4. Poliomyelitis.
5. Lymphocytic Meningitis.
6. Syphilitic Meningitis.
7. Brain Abscess.
8. Subarachnoid Haemorrhage.

Typical Case of Tuberculous Meningitis

J. B., a male of 23 years was admitted to hospital on 6.11.40 with a history of headache and vomiting which began six days previously. He had no history of any serious illness and had not had any complaint relating to the chest or abdomen. There was no family history of pulmonary tuberculosis.

Clinical Examination.

The patient was a well developed and well nourished male. He complained of a persistent but not severe frontal headache.

Nervous System.

On admission there was no nuchal rigidity.
Kernig's sign was negative.
The pupils were equal and reacted to light.
Knee jerks both present.
Plantar reflexes flexor.

Chest.

There was no dulness to percussion.
The breath sounds were vesicular.
A few scattered rhonchi were heard in both lungs but no evidence of active disease could be found.

Other Systems.

No evidence of disease.

The patient was lumbar punctured on admission - the sixth day of illness.
The fluid was clear and contained 300 cells per cu.mm.
The majority of the cells were lymphocytes.
On standing, a web formed and this was examined for tubercle bacilli but no organisms were found.
The protein content was moderately increased.
Only a trace of sugar was present.
The chloride content was 620 mgm. per 100 cc.
The Tryptophan Test gave a typical positive reaction.

History while in Hospital.

On the 8th day of illness the patient developed a slight nuchal rigidity and Kernig's sign was positive.
The patient was not drowsy on admission but by the 9th day of illness this symptom began to appear and he became slightly confused.
The Mantoux Test was found to be positive, but the Tuberculine Patch Test showed no reaction.
Drowsiness became gradually more marked and the patient died on the 15th day of his illness.
The patient did not vomit on any occasion during the entire stay in hospital.

A post mortem examination was performed and the following features were noted:-

Lungs.

A healed tuberculous lesion was found in the apex of the right lung. The lesion was 2 cm. in diameter and the cut surface showed some evidence of caseation. The hilar glands in relation to the upper lobe of the right lung were enlarged and caseous.

Spleen.

The organ was firm and of normal size. A section was taken for microscopical examination.

Other Organs.

No pathological change was found in the liver, pancreas, adrenal glands or alimentary tract.

Brain.

The durameter was found to be slightly adherent to the underlying leptomeninges over the right pariental area.
An excess of clear cerebro spinal fluid was found in the ventricles.
In the leptomeninges at the base of the brain and along the course of the surface blood vessels, especially those in the fissure of Sylvius, numerous miliary tubercles were found.

A small pressure cone was formed on the under surface of the cerebellum but the convolutions were not unduly flattened.
Exudate was present at the base of the brain and miliary tubercles were also found on the choroid plexuses in the lateral ventricles.
No lesion was found in the substance of the brain.

Sections were taken from the brain, spleen and a lymphatic gland at the root of the right lung for microscopical examination.

Brain.

In relation to the blood vessels on the surface of the brain there was a marked degree of round cell infiltration. In several of the infiltrated areas, caseating necrosis had occurred. The walls of the blood vessels were thickened. No change was found in the substance of the brain.

Spleen.

A small number of areas of caseating necrosis were found in the substance of the spleen.
Multinucleated giant cells were seen in two of these areas.
Thickening of the walls of the blood vessels was a marked feature.

Lymphatic Gland.

Numerous areas showing caseating necrosis were present throughout the gland.
A considerable number of multinucleated giant cells were seen in these areas.

The main points of interest in this case are

1. The characteristic history of onset with headache and vomiting
2. The absence of definite signs of meningeal irritation on admission to hospital.
3. The appearance of nuchal rigidity and a positive Kernig's reaction on the 8th day of illness.

4. The absence of the tubercle bacillus in the cerebro spinal fluid which was, however, characteristic in all other respects.
5. The typical post mortem features of tuberculous meningitis.

Meningismus.

This condition is usually seen in children in association with some acute condition such as pneumonia or enteritis.

The fluid is found to be normal in all respects although occasionally the chloride content may be low as a result of vomiting.

A Case of Pneumonia with Meningismus.

The patient, J. B., a boy of 8 years, was admitted to hospital on 16.10.40 in his second day of illness.

On admission his temperature was 103.4° F. and his pulse rate 136 per minute. The respirations were 32 per minute.
He complained of headache and was delirious.
He vomited on several occasions.
On examination nuchal rigidity was found to be present and Kernig's sign was also positive.
Examination of the chest revealed consolidation in the mid zone of the right lung.
The breath sounds in this area were tubular in character and moist crepitations were also present.
A lumbar puncture was performed on admission and the cerebro spinal fluid was found to be normal in all respects.
The cells numbered 5 per cu. mm.
The protein content was normal.
The sugar content was also normal.
The chloride estimation was 740 mgm. per 100 cc.
The Tryptophan Test was negative.

The patient was treated with Sulphapyridine (M.&B.693) and by the second day after admission the temperature had settled to normal, vomiting and headache had disappeared, there was no nuchal rigidity and Kernig's sign was now negative.

By 25.10.41 (nine days after admission), the clinical signs of pneumonia had disappeared from the chest and the patient made an uneventful recovery.

Septic Meningitis.

The fluid is usually quite turbid when withdrawn and on microscopic examination, numerous polymorphs and probably micro-organisms are observed. Difficulty may arise where the attack of meningitis is mild and is clearing up when the case is first observed. In these cases the fluid may be clear or only slightly turbid. The cell count is frequently within the limits expected in tuberculous meningitis but the type of cell is found to be chiefly polymorphonuclear. The sugar content is helpful because at this stage it has usually returned to normal or may actually be increased.

Poliomyelitis and Encephalitis.

In these conditions the cell count is usually only slightly higher than normal. Sometimes, however, it is found to fall within the range expected in tuberculous meningitis. The lymphocytes predominate. The protein content is above normal but seldom within the range seen in tuberculous meningitis. Most help is obtained from the estimation of the sugar and chlorides which in these conditions are usually normal but may be slightly upset. Both the Tryptophan Test and the Levinson Test may be positive.

Typical Case of Acute Anterior Poliomyelitis.

R. C., a boy of 16 years, was admitted to hospital on the sixth day of his illness. This started with shivering and vomiting accompanied by severe pain in the dorsal region of the back. The following day he was found to have paralysis of both legs and weakness of the left arm.

Clinical Examination

On admission the temperature was 102°F. and the pulse rate was 106.

The respiration rate was 34 and the patient was slightly cyanosed suggesting some degree of involvement of the intercostal muscles.
The muscles of both legs were completely paralysed and no knee jerks were present.
The plantar reflex was not elicited.
The left arm was weak but some movement was still present; the tendon reflexes, however, were absent.
There was, however, no paralysis of the muscles of respiration.

The patient was lumbar punctured on admission and the cerebro spinal fluid was found to be clear and not under pressure.
The cells were chiefly lymphocytes and numbered 55 per cu. mm.
The protein content was 40 mgm. per 100 cc.
The sugar was normal in amount and the chlorides were 700 mgm. per 100 cc.
The Levinson Test and Tryptophan Test were both positive.
For the first few days Kernig's sign remained positive.
Nuchal rigidity was not marked but flexion of the head caused severe pain in the back.
The paralysed muscles remained tender to pressure for about 7 days.
The sensations were never found to be impaired.

The temperature and pulse rate settled to normal by the end of the second day in hospital and remained normal thereafter.

The paralysis of both legs and the paresis of the left arm have persisted and are flaccid in type.

An Interesting Case of Poliomyelitis.

The patient, M.R., a male of 10 years, was admitted to hospital on 15.7.41 as a case of poliomyelitis and pneumonia.

History.

On 13.7.41 the patient complained of severe headache but was otherwise well.
On 14.7.41 the patient was seen by his own doctor

and was found to have paralysis of both arms.
A diagnosis of poliomyelitis was made.
On 15.7.41 the doctor was again called and on this occasion he found the patient to be very breathless. A diagnosis of pneumonia was made and the patient was sent to hospital immediately. The patient was admitted to hospital at 4.10 pm. and died 45 minutes later.

On arrival in hospital the patient was found to be very breathless and cyanosed.
The respiration rate was 40 per minute and the pulse and temperature 104 and 100.6°F. respectively.
He was quite conscious on admission.
Both arms were completely paralysed but there was no involvement of the legs.
Paralysis of the intercostal muscles and diaphragm were complete and respiration was being carried on entirely by the muscles of the neck.
Oxygen and artificial respiration were administered until a Drinker respirator could be obtained from a near-by hospital but the child died just prior to the arrival of the apparatus.

A cisternal puncture was performed immediately after death and a clear fluid was obtained.
The cells numbered 267 per cu. mm. and were mainly lymphocytes.
The sugar content was normal.
The protein amounted to 30 mgm. per 100 cc. and the chloride content was 700 mgm. per 100 cc.

Lymphocytic Meningitis.

Acute lymphocytic meningitis is a specific disease which has been described in recent years. It is characterised by the signs and symptoms of meningeal irritation, the cerebro spinal fluid has certain distinctive features and the condition usually ends in complete recovery.

The disease has been shown to be due to a virus infection. Armstrong and Dickens (1935) succeeded in isolating the virus from the cerebro spinal fluid in a series of cases and the virus was found to be pathogenic both to the monkey and the mouse.

The disease frequently begins with the symptoms of an upper respiratory tract infection and the patient develops intense headache.
Nuchal rigidity is present and Kernig's sign is positive.
The temperature is elevated at the onset but falls to normal within a few days.
The cerebro spinal fluid is clear when withdrawn at lumbar puncture.
The cell count is increased to a variable extent. Armstrong and Dickens record the increase as varying from 50 to 2000 cells per cu. mm.
The cells are 90 to 100% lymphocytes.
The protein content is increased but never to the extent found in tuberculous meningitis.
The sugar content is usually normal and is never greatly diminished as is the case in tuberculous meningitis.
The chloride content is unaltered.

Several diseases have as one of their features an increase in the number of lymphocytes in the cerebro spinal fluid. Beacuse of this, the name lymphocytic meningitis is perhaps unfortunate in its choice. The presence of meningeal irritation together with a clear cerebro spinal fluid containing an increased lymphocyte cell count makes this condition resemble closely the condition of tuberculous meningitis. The differential diagnosis is greatly facilitated, however, by the biochemical findings. The protein is not usually increased to the extent found in tuberculous meningitis and the sugar and chloride contents are usually normal.

Birch (1936) has described a series of cases occurring in this country and Hughes (1937) described two of a series of cases seen in Malaya.

A Typical Case of Lymphocytic Meningitis.

J. F., a boy of 13 years was admitted to hospital on his second day of illness. He complained of severe pain in the head and the back of the neck, as a result of which his doctor sent him to hospital as a case of cerebro spinal fever.

Clinical Examination.

On the arrival of the patient in hospital he was examined and found to be moderately ill.
His temperature on admission was 100° F and his pulse rate 106.

Nervous System.

Patient had a marked nuchal rigidity and Kernig's sign was also positive.
Pupils were equal and reacted to light.
Tendon reflexes were active.

Other Systems.

All other systems were found to be normal.

He was lumbar punctured on admission and the fluid was clear and not under pressure.
No web formed on standing.
The cells numbered 309 per cu. mm. and the vast majority were lymphocytes.
The protein content was increased to 40 mgm. per 100 cc.
The sugar was also slightly increased, a yellow precipitate being obtained on boiling.
The chlorides were 680 mgm. per 100 cc.

Progress in Hospital.

No treatment was prescribed but the second day after admission the temperature had fallen to normal and the pulse rate came down to 80.
Nuchal rigidity and Kernig's sign persisted for about one week and the patient was again lumbar punctured.
On this occasion the fluid was again clear.
There was no web formation and the cell count had fallen to 22 cells per cu. mm.
The protein estimation was 30 mgm. per 100 cc.
The sugar content had now returned to normal and the chlorides had risen to 730 mgm. per 100 cc.
The boy was now perfectly well but was kept under observation for a further 10 days after which he was dismissed from hospital as cured.

Syphilitic Meningitis.

The presence of a positive Wasserman Reaction in the cerebro spinal fluid is diagnostic in this condition. The protein may be increased and an increased lymphocyte count may be present.

Brain Abscess.

An abscess in a silent area of the brain which gives rise to no localising symptoms occasionally causes difficulty in differential diagnosis.
The cells are increased over a wide range but are frequently polymorphonuclear in type.
The protein is also increased - usually slight but may be increased within the range of tuberculous meningitis.
The sugar is usually diminished.
The chlorides are usually normal and may actually show a marked increase.

A Case of Brain Abscess.

The patient, J.L., a boy of 10 years, was admitted to hospital in his third day of illness.
On admission he was classified as acutely ill and complained of headache and vomiting. The temperature was 97° F. and the pulse rate was 66.
The patient was drowsy, nuchal rigidity was present and Kernig's sign was positive.
The right knee jerk was present and the left was absent.
The plantar reflexes were both flexor.
The pupils were equal and reacted to light.
Examination of the fundi showed papilloedema to be present.
There was no localising paralysis and no history of a discharging ear.

Course of the Disease.

The temperature remained normal throughout but the pulse rate rose rapidly to 150. The child's condition deteriorated and the patient died on the 6th day of illness.

Investigation of the Cerebro Spinal Fluid.

The patient was lumbar punctured on admission (i.e. on the 3rd day of illness) and again on the 5th day of illness.

The first speciemn showed an increase in the cell count to 20 per cu. mm. - these appeared to be chiefly lymphocytes.
The protein was normal - 20 mgm. per 100 cc.
The sugar content was normal.
The chlorides were reduced to 650 mgm. per 100 cc.

In the second specimen, the cell count was found to be 11 per cu. mm.
The protein showed a slight increase to 30 mgm. per 100 cc.
The sugar content was slightly increased.
The chlorides were now 660 mgm. per 100 cc.

Post Mortem Examination.

The only abnormality found was in the central nervous system. The convolutions of the brain were flattened and when the substance of the brain was sectioned a large abscess, about $1\frac{1}{2}$" in diameter was found in the left occipital lobe.

Subarachnoid Haemorrhage.

Examination of the cerebro spinal fluid in this condition reveals xanthochromic staining. The question sometimes arises as to whether there is also a tuberculous meningitis present.

The cell count is valueless because of the presence of numerous erythrocytes.
The protein content is completely upset by the presence of blood serum in the fluid.
The sugar and chloride contents, however, are of considerable value because in subarachnoid haemorrhage these are usually normal or slightly increased.

Posterior Basic Meningitis.

It may be found impossible to distinguish this condition from tuberculous meningitis by examination of the cerebro spinal fluid and clinical features must be relied upon for a differential diagnosis. In many cases, however, a purulentfluid containing meningococci will have been obtained in the early stages of the disease.

A Case of Chronic Meningitis (Posterior Basic Meningitis.)

W. S., an infant of six months, was admitted to hospital as a case of cerebro spinal fever. The child was vomiting and there was rigidity of the neck muscles. The patient was lumbar punctured and a turbid fluid was obtained. A film was made from the centrifuged deposit and this showed numerous polymorphonuclear leucocytes and gram negative diplococci.

Treatment with sulphanilamide was instituted.
The temperature settled within a few days but despite the treatment the child's general condition failed to improve.
After two weeks the child was again submitted to lumber puncture.
The cerebro spinal fluid on this occasion was found to be clear.
The protein content showed a marked increase.
The sugar was slightly diminished in amount.
The chloride estimation was 690 mgm. per 100 cc.
Both the Levinson and Tryptophan Tests were positive.

By this time the infant had lost a great deal of weight, vomiting continued and opisthotonus was now a marked feature. The general condition continued to deteriorate and after a further week the child was again lumbar punctured.

The fluid was found to be clear and under pressure.
No organisms were found.
The cells numbered 110 per cu. mm. and these were chiefly lymphocytes.
The protein content was increased to a marked degree.
The sugar was diminished but not completely absent.
The chloride content was 660 mgm. per 100 cc.
Both the Levinson and Tryptophan Tests were positive.

The child eventually died after an illness of approximately 5 weeks duration.

The interesting feature of the case is that after treatment with sulphanilamide the fluid lost its turbidity and developed all the characteristics which one finds in the cerebro spinal fluid from a case of tuberculous meningitis. The differential diagnosis between these two conditions, therefore, depends on clinical observations chiefly unless one is fortunate enough to have examined the fluid in the early stages of the disease when meningococci were present.

Conclusions.

The only absolute criterion for the early diagnosis of tuberculous meningitis is the finding of the tubercle bacillus in the cerebro spinal fluid. If care is taken and time is spent on the investigation, I believe that the organism can be demonstrated in over 70% of cases on the first occasion at which the fluid is obtained.

Higher percentages of positive results can, no doubt, be obtained by guinea pig inoculation, but the value of this procedure is lost because of the fact that the patient is dead long before the result is available.

Culture of the organism has the same disadvantage in that no growth is seen for at least 10 days.

No single biochemical test or other procedure can in itself be said to be diagnostic of tuberculous meningitis.

If the cell count lies between 40 and 500 cells per cu. mm. with a high percentage of lymphocytes, then this is suggestive of tuberculous meningitis, but might equally well be lymphocytic meningitis, encephalitis or poliomyelitis.

Diminution of sugar and chlorides is found in other conditions besides tuberculous meningitis.

The increase of protein is also found in several different conditions.

The Tryptophan Test and the Levinson Test which have been claimed to be diagnostic of tuberculous meningitis are found to give positive results in other conditions as well.

If all the tests which I have described were carried out on suspected fluids there would be no difficulty in arriving at a conclusion as to whether or not the case was one of tuberculous meningitis. This unfortunately, is a lengthy procedure and is certainly not suited to the scope of the general practitioner nor is it convenient for the average

hospital physician who does his own biochemistry. A short cut to diagnosis is desirable and I have come to the conclusion that the following investigations are all that is necessary in the majority of cases.

A thorough search should be made for the tubercle bacillus in the coagulum which forms in the fluid on standing. This is absolute evidence of the nature of the disease. About 24 hours, however, is required for the web to form before this examination can be carried out but a reliable opinion can be expressed at once by carrying out the following steps.

1. A cell count should be made and the predominant type of cell observed.

2. The protein content should be estimated.

3. The amount of sugar present in the fluid should be ascertained by qualitative methods.

The cell count should lie between 40 and 500 cells in the majority of cases. Lymphocytes should predominate.

The protein content as estimated by the proteinometer should have a minimum value of 50 mgm. per 100 cc.

The sugar content as estimated by the qualitative method should be diminished or absent.

Such a procedure can be carried out with ease in 15 minutes and the results are most reliable.

The only condition which may cause trouble in the differential diagnosis is posterior basic meningitis and this condition must be recognised clinically.

SECTION V.

PROGNOSIS IN TUBERCULOUS MENINGITIS.

For all practical purposes, tuberculous meningitis can be stated to have a fatal termination in 100% of cases. This statement is not absolutely correct because, from time to time, cases of recovery have been recorded. In the last 10 years, at least three cases have been published in the literature in this country which appear to me to justify the claim of recovery from this condition.

Parry records a case where the first symptom was tonsillitis. Six days later headache developed together with ptosis of the eyelids. Kernig's sign at this stage was negative but pain was experienced when the head was bent forward. The following day the patient was semi-comatose, nuchal rigidity was present and Kernig's sign was positive. A lumbar puncture at this stage produced clear fluid under pressure. The cell count was increased and lymphocytes were in excess. Globulin was present in excess and the tubercle bacillus was found in the clot which formed on standing.
One week later the headache had disappeared.
The patient was quite well when seen four years later.

Hobson records a case admitted to hospital with a history of joint pains of 6 weeks' duration and stiffness of the neck of 2 week's duration. The main features of the case were the presence of headache and vomiting together with deafness. Nuchal rigidity was marked and Kernig's sign was positive.

The cerebro spinal fluid was examined on several occasions and the findings are set out in the following table.

Date	Organisms	Protein	Cells	Chlorides
11/7/1934	T.B. +ve	+++	Increased	620 mgm.
13/7/1934	T.B. +ve	+++		550 mgm.
26/7/1934	T.B. -ve		Increased	620 mgm.
30/7/1934	T.B. +ve		Increased	630 mgm.
12/8/1934	T.B. -ve	+++		680 mgm.
14/8/1934	T.B. -ve			
31/8/1934	T.B. -ve	+++	Polymorphs	690 mgm.
/3/1935	T.B. -ve	Trace		800 mgm.

As shown above, the tubercle bacillus was found on three separate occasions.

The Wasserman Reaction was negative and a radiograph of the chest showed a healed focus in the left lung. The patient recovered, and as shown in the table the fluid was normal when examined seven months later.

McGuinness records a case of a woman who was admitted to a mental institution suffering from acute confusinal psychosis. The patient had received an injury to the back of the head as a result of a fall 3 days before admission. 12 days later, as a result of persistant drowsiness, headache and irritability, a lumbar puncture was performed.

Pus cells, chiefly lymphocytes, were found to be present and the tubercle bacillus was demonstrated.
Six days later the physical signs of meningitis had disappeared.
After a further 5 days, the patient was again lumbar punctured. The lymphocytes were again increased.
Globulin was present in excess but the tubercle bacillus was not demonstrated.
Four months later, a specimen of cerebro spinal fluid was found to be normal and the patient was perfectly well.

A Case of Miliary Tuberculosis and Some Degree of Meningeal Involvement with Recovery.

The patient, J. McG., a male of 15 years, was admitted to hospital on 27/9/40 as a case of pneumonia. He was in his eighth day of illness and complained of cough, vomiting and pain in the right side of the chest. The temperature was intermittant in type and the only abnormality noted on clinical examination was the presence of a few crepitations in the right auxilla.

The patient was X-rayed on 30/9/40 and pleural thickening was found to be present in the upper half of the right lung. About this time, the patient began to show signs of mental upset. At times he was noisy and outrageous and at other times he was drowsy. A lumbar puncture was performed on 4/10/40 and the protein content showed a slight increase together with a slightly positive Tryptophan Reaction. The sugar was normal and no web formed on standing.

Examination at this stage revealed the presence of crepitations throughout the left lung and an X-ray taken on 9/10/40 was reported on as follows-
"The pleural thickening seen in the right lung has now cleared up but the appearance is now suggestive of early miliary tuberculosis.

The intermittant temperature persisted and a Widal Blood Test was found to be negative for B. Typhosus and B. Paratyphosus. The chest was again X-rayed on 19/10/40 and the appearance was reported as being very suggestive of miliary tuberculosis. On 22/10/40 the Mantoux and Tuberculine Patch Tests were performed and both gave a well marked positive reaction.

A further X-ray of the chest was performed on 29/10/40 and the typical appearance of miliary tuberculosis was found to be present. On the same day, the patient, who was now more rational, was again lumbar punctured and the fluid was found to be normal except for a slight increase in the protein content. Examination of the fundi showed the presence of early papilloedema.

The temperature began to settle at the end of the third week although crepitations still persisted in the lungs. The sputum which was examined on several occasions was always negative for the tubercle bacillus.

A radiograph of the chest on 11/11/40 again showed the typical appearance of miliary tuberculosis, but a further examination of the chest on 26/11/40 showed definite improvement in the appearance of the lung fields, although not yet normal. At this stage the boy was clinically well, the temperature and pulse were normal and no adventitious sounds could be heard in the lungs.

A radiograph taken two months later showed no abnormality in the chest and the boy has remained in good health since.

These cases prove conclusively that an occasional recovery does take place, and this is specially well demonstrated by the case recorded by Hobson where the tubercle bacillus was found in the fluid on three separate occasions.

Three cases of recovery are recorded by MacGregor but they are not so convincing as the ones recorded in detail for two main reasons. In the first place none of the cases were typical from the clinical point of view. Secondly, the tubercle bacillus was never found in a direct film made from the cerebro spinal fluid but only proved positive after guinea-pig inoculation.

In brief, it might be stated that although a few cases of recovery have been recorded, in the vast majority of cases, the prognosis is uniformly fatal.

SECTION VI.

TREATMENT OF TUBERCULOUS MENINGITIS.

Since the disease is fatal in the vast majority of cases, the question of prevention is of prime importance in this condition. It has been shown pathologically that practically all cases of tuberculous meningitis have a pre-existing tuberculous focus elsewhere in the body and consequently the problem of prevention of tuberculosis in any form is the most important aspect. This is a wide subject and involves the questions of better housing, improved feeding and the provision of adequate hospital accommodation for the treatment of active cases.

It has also been shown that a significant percentage of the cases of tuberculous meningitis observed in this series can be traced to contact with a pulmonary case of tuberculosis in the same family. This occurs so frequently in infants where the mother is suffering from pulmonary tuberculosis that some action should be taken for its prevention.
Two methods of dealing with the problem can be adopted:-

1. The mother can be removed to a sanatorium where the disease may be rendered inactive by treatment and, of more importance, she will be prevented from transmitting the disease to others.
2. The child may be removed from the infected mother immediately after birth. In most cases, the family concerned can arrange for a relative to look after the upbringing of the child but, if necessary, the local authority should be prepared to make provision for such cases.

The treatment of an actual case of tuberculous meningitis has, as its chief object, the prevention of suffering in a disease which is fatal. Repeated lumbar puncture may be performed to relieve the intense headache and this may be supplemented by the administration of morphia. When the patient passes into the drowsy stage, the senses are considerably dulled and active measures are no longer necessary.

FINAL CONCLUSIONS

Tuberculous meningitis is a disease seen chiefly in children, especially in the first five years of life. The incidence is slightly greater among males and it is greatest in the second quarter of the year. The chief factor in the etiology of the disease is contact with a case of open pulmonary tuberculosis and this frequently takes place within the family circle. (See Page 21)

From the pathological point of view, it has been found that practically all cases have a pre-existing tuberculous focus elsewhere in the body, and this is most frequently found to be an inactive lesion in the lungs or the associated lymphatic glands.

Clinically the disease is very difficult to diagnose in its earlt stages, and, as a result, examination of the cerebro spinal fluid is of prime importance.

If the tubercle bacillus can be demonstrated in the web which forms when the cerebro spinal fluid is allowed to stand, then an absolute diagnosis can be made within 24 hours. In the vast majority of cases, however, a diagnosis can be arrived at immediately by carrying out three simple procedures.

1. Enumeration of the cells and an estimation of the type of cell which predominates.

2. Estimation of the protein content.

3. Estimation of the sugar content by the qualitative method. (See Page 101)

Having arrived at a diagnosis, the treatment consists of making the patient as comfortable as possible until death supervenes, as the prognosis is practically always fatal.

REFERENCES.

Aiello (Quoted from Spillane).

Armstrong, C. & Dickens, P.F. (1935) Quoted from Hughes.

Baxter, H. Trans. of Tub. Soc. of Scot. (1936-7) pp. 11-16.

Birch, C.A. Practitioner (1936) 137, 219.

Blacklock, J.W.S. & Griffin, M.A. Jour. of Path. & Bact.40: 489-502.

Brown, W. Trans. of Tub. Soc. of Scot. (1933-4) pp. 26-30.

Brugi, (Quoted from Spillane).

Clark, G. Trans. of Tub. Soc. of Scot. (1933-4) pp. 46-53.

Currie, J.R. Textbook of Hygiene p. 553.

Giustra, F.X. J. Pediat (1937) 11, 805-811.

Greenfield, J.G. Clinical Interpretation of Aids to Diagnosis. (1930) Vol.I. p. 47.

Halliday, J. Trans of Tub. Soc. of Scot. (1924-5) pp. 66-74.

Harrison, G.A. Chemical Methods in Clinical Medicine. (1939) p. 393.

Hemenway Amer. J. Dis. Child. 1, 37.

Hendry, E. Arch. Dis. Childh. (1939) 14, 307.

Hobson, F.G. Lancet (1935) 1:933-4.

Hughes, W. B.M.J. (1937) 1:1063-5.

Hurwitz, S. Tubercle (Dec.1937) 19:127-129.

Ingham, J. B.M.J. (1937) 2:111-113.

Kinnear, W.L. Lancet (1925) 1: 19.

Laidlaw & MacFarlane B.M.J. (1941) 2: 436-7.

Lichtenberg, H.H. Amer. J. Dis. Child 43. 32.

McCracken, I. Trans. of Tub. Soc. of Scot. (1933-4) pp. 31-37.

Macgregor, A. Trans. of Tub. Soc. of Scot. (1933-4).

Macgregor, A.R. & Green, C.A. J. Path. & Bact. 45. 613-645.

McGuinness B.M.J. (1937) 1: 169.

McNeil, C. Br. Journal of T.B. (July, 1932).

Messeloff, C.R. J. Pediat 1: 349 (1932).

Newman, K.O. Lancet (1938) 1: 1333.

Ogilvie, A.G. Br. Journal of T.B. (July, 1932).

Parry, C.L. B.M.J. (1934) 2: 859-860.

Rich & McCordock (Quoted from Macgregor & Green).

Schumacher (Quoted from Spillane).

Spillane, J. Lancet (1937) 1,560-561.

Stewart, C.P. & Dunlop, D.M. Clinical Chemistry in Practical Medicine. (1937) p. 234.

Stewart, D. Trans. of Tub. Soc. of Scot. (1926-7).

Weichsel, M. & Herzger, G. Jour. of Pediat (1936) 9: 763-770.

Wilson, S.R. Br. Jour. of T.B. (July, 1932).