THESIS

on

SOME CASES of EPIDEMIC ENCEPHALITIS

Presented for the Degree of Doctor of Medicine of

THE UNIVERSITY of EDINBURGH.

by

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A CLINICAL SURVEY

OF

SOME CASES OF EPIDEMIC ENCEPHALITIS.
The epidemic of Encephalitis Lethargica, in association with which were the cases to be described, occurred in the City of Sheffield mainly in the winter months and spring of 1924.

As the number of notifications was so great, it was found impossible to deal with all the cases in the General Hospitals; and it was therefore decided that two wards in Lodge Moor Fever Hospital should be set aside for their reception. These wards were constantly occupied from the beginning of April until about the middle of October, the last notified case being admitted to hospital on September 26.

I had, therefore, while resident at Lodge Moor Hospital, the opportunity of observing 127 cases of true Epidemic Encephalitis. This represents the number of cases of actual Encephalitis out of a total of 176 admitted to this hospital already diagnosed as such, in addition to five cases notified as other diseases, that were found, after admission, to be suffering from Encephalitis.

EPIDEMIOLOGY

I am indebted to the Department of Public Health for the following table, which illustrates the monthly incidence of the disease, and the number of deaths in the City of Sheffield from the beginning of
the epidemic in January until October, 18, 1924, many cases being treated in other institutions or in private.

- TABLE -

<table>
<thead>
<tr>
<th>Month</th>
<th>Notification</th>
<th>Deaths</th>
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<tbody>
<tr>
<td>Jan.</td>
<td>..</td>
<td>1</td>
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<tr>
<td>March</td>
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<td>26</td>
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<tr>
<td>April</td>
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<td>121</td>
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<tr>
<td>May</td>
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<td>91</td>
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<td>June</td>
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<td>August</td>
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<td>18</td>
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<td>September</td>
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<td>6</td>
</tr>
<tr>
<td>October</td>
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<td>7 Including 319 (1 Polio Enceph.) 32</td>
</tr>
</tbody>
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This demonstrates the main incidence to have been in the months of April and May, being a little later than the usual seasonal incidence in the winter months, but following sufficiently closely to be characteristic and in contrasting with the seasonal incidence of Poliomyelitis.

As diagnosis may sometimes be extremely difficult, some of the above number of cases were almost certainly not cases of Epidemic Encephalitis; but on the other hand, it probably does not include some mild or abortive cases, especially as during this/
this epidemic, particularly in the latter part, many cases of a mild character must have occurred.

Analogous to this are the results given by the tabulating of the series of 127 cases treated in Lodge Moor Hospital (omitting those cases wrongly diagnosed), not only in the seasonal incidence, the ratio of deaths to the number of cases notified, but also in the mortality rate.

<table>
<thead>
<tr>
<th>Month</th>
<th>Number of Cases admitted</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>March</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>April</td>
<td>57</td>
<td>6</td>
</tr>
<tr>
<td>May</td>
<td>40</td>
<td>4</td>
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<td>June</td>
<td>11</td>
<td>1</td>
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<tr>
<td>July</td>
<td>13</td>
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<td>August</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>September</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>127</strong></td>
<td><strong>13</strong></td>
</tr>
</tbody>
</table>

**Mortality**

While all the facts are not yet to hand, it is certain that the figures given represent quite accurately the mortality, which in each case is seen to be a little above ten per cent. This is lower than the usual mortality in epidemics, which has varied from/
from about fifteen per cent to fifty per cent, but can be explained by the number of mild cases which were dealt with.

In the earlier part of the epidemic there occurred a greater number of cases of a severe type than in the later part, which accounted for most of the deaths. For example, out of twenty-one cases in the Royal Infirmary between 10th March and 21st May, four died. At the same time it must be noted that this occurred at the period of highest incidence in the disease; and probably merely serves to show, as was my experience, that the virulence of the epidemic was more profound during the sharp increase of numbers in April and May, and became gradually exhausted as the disease lessened in the late summer and autumn months.

Out of 13 deaths, 6 occurred in cases above the age of 30 and below the age of 55 -- 4 between the ages of 10 and 30 and 3 below the age of 10. The lowest age at which death occurred in my series of cases was 6, and the highest 52 years.

SEX and AGE INCIDENCE: Out of the 126 cases, to which alone I now refer, 83 were males and 43 females. This is by no means the usual experience in epidemics, but has been recorded before.
All ages were represented, but very few at the extremes of life. There was only one case above the age of sixty, and two below five.

With regard to the latter, the common occurrence was to mistake Tuberculous Meningitis and Miliary Tuberculosis for Encephalitis in very young children. This, coupled with the fact that among my cases there were only two children whose ages were below five, has led me to consider a diagnosis of Encephalitis at that age with great suspicion until the exclusion of other conditions, especially the two mentioned above, as they may simulate it very closely.

The majority of cases occurred among older children and those in early adult life. Almost fifty per cent were between the ages of 6 and 20; and those between 20 and 35 represented slightly below thirty two per cent. Above the age of 35 each decade was represented by an almost equal and small number of cases up to the age of 80.

Occupation: The greater number of the cases admitted were naturally drawn from the poorer classes of society. The disease occurs, however, quite irrespective of occupation or social conditions.

Encephalitis in Pregnancy: I had under my care three women who all suffered from a severe attack of the/
the disease, and who were all far advanced in pregnancy. While no conclusions can be based upon the observation of such a few, I did not find that their condition had any appreciable effect upon the course of the illness. One case was complicated by an old-standing mitral lesion.

All made a good recovery, and were discharged apparently well; while one gave birth at full term, when still in hospital, to a normal healthy child. Each had been a typically severe case, and never at any time showed signs of abortion; while in the other two, at the time of discharge from hospital, the fetus was living.

In this connection it is of interest to note that one of these cases later became possessed of homicidal tendencies, and made a furious assault upon her husband; but at the same time, it has to be remembered that such a happening is unfortunately common among the sequelae of Encephalitis.

**Infectivity : Incubation Period :**

It is known that Epidemic Encephalitis may be spread by contagion, but among my cases I have only been able after enquiry to demonstrate one where there was a history of exposure to the disease. The case also/
also demonstrates the possibility of familial infection.

The case to which I refer was one of a girl aged seven, exhibiting an intense choreo-athetotic type of the disease, who died after an illness of fourteen days. The father of this child fell ill on March 22, complaining of headache which became very severe. He had delusions and in a few days developed myoclonus. Death took place on March 30. The child first fell ill on April 16. There could be little doubt that in the case of the father death was due to Encephalitis, while the cause of the child's death was proved by post-mortem examination.

Though this was the only case where I was able to show that there had been any possibility of infection, it is of interest to note that I have been informed that some children in the families from which a few of my young cases came had suffered from Chorea. Considering that there is a very definite Choreiform type of this disease, it is feasible that other cases may have been infected by contact with cases of supposed Chorea, which in reality have not been recognised as suffering from Encephalitis. Unfortunately, I have had no opportunity of fully investigating this aspect of the question.

Incubation Period:

Coincident with the lack of data regarding/
regarding contagion has been the impossibility of obtaining details for the estimation of the incubation period. The example of familial infection quoted above affords the only means for its estimation among my series of cases. Consideration of the dates given will show that the incubation period in the case of the child may have varied from two or three days up to twelve days, or even more.

The experience of lack of details as to definite or obvious contagion is general; but outbreaks in the same house or institution have occurred.

Re-infection:

The chronic type of Encephalitis is now well recognised, and particular attention is drawn to those cases where recrudescence occurs a varying length of time after the initial attack. There can be no doubt that after infection has taken place the virus may remain quiescent over a long period until by some means it is again stirred into activity. This auto-infection is quite a characteristic feature and I have had several cases which have illustrated it quite definitely. One of my cases first had an attack in 1921, and recovered to again fall a victim in 1924, being well during the intervening years. One or two others have had second attacks several months after what was known to be their first illness of/
of this kind.

Such cases in addition to re-infecting themselves, may act as a source of infection to others, and may almost be regarded as carriers; as, if the virus may remain capable of causing a fresh attack in the original person, it is not unreasonable to assume that it may be transferred by them to others, to cause the disease in whatever may be the suitable conditions.
CLASSIFICATION:

Various attempts have been made to classify the types of this disease, and since its first recognition many and varied schemata have been put forward.

That a standard classification is impossible is at once seen now that it has been shown how the disease varies in each successive epidemic. It is manifestly also impossible to formulate groups according to some predominant symptom, as such symptom may also occur in cases named in another group; so that for such cases it would be necessary to create an entirely new group, thus producing an unnecessary confusion.

I do not, therefore, propose to endeavour to classify the various types which have come under my notice; but several predominant types deserve further discussion.

The cases fell naturally into three main divisions, according to virulence and the mode of onset.

(I.) Fulminating: A few showed evidence of intense virulence of attack, and proved fatal in a very short space of time. In two cases death took place within four days of the first sign of illness.
illness; while three others died at the 8th., 10th., and 11th day of disease. Every one was obviously destined to be fatal from the high degree of toxæmia present.

(II.) Acute:

Under this heading came a number where the onset was sudden, and the attack was for a time of a serious nature. While not nearly so numerous as the next type, the patients in this group furnished the greater number of good recoveries; the remainder gradually assumed the characteristics of the chronic disease.

(III.) Chronic:

By far the greater number of cases made up this group, and are so classed owing either to an insidious onset or to the persistent nature of some symptoms. It includes also those cases which, after an acute illness, drifted into a chronic stage.
CLINICAL FEATURES

Mode of Onset:

The actual onset varies practically with every individual. The disease may commence with appalling suddenness, or may appear so gradually that the condition is not recognised until well established.

Any one of a variety of symptoms may first demand attention, in those cases where the onset is sudden. Epileptiform seizures, headache and neuralgic pains, aphasia, hemiparesis, and states of mental confusion may be the first symptoms. In one case under my care, a young man, the illness commenced with violent epilepsy which lasted for twenty four hours, after recovery from which definite myoclonus and other symptoms remained. In another, a young married woman, the first sign was an attack of a peculiar respiratory spasm, associated with sobbing, which persisted over several hours; while a boy was taken for a doctor’s advice, as he had been discovered 'taking the cat for a walk in the street at two o'clock one morning'! One man, who quickly recovered, had sudden aphasia, followed shortly by agraphia, some degree of mental confusion, and right-sided weakness; and another patient, while walking along a drive, felt dizzy,
dizzy, and found that he then saw all objects double.

Cases such as these are not very common, yet the positive statements of the patients leave no doubt as to their occurrence.

The majority of cases are of a slow or insidious nature, or may commence in such a fashion that a diagnosis of some other disease has been made. In this respect, quite a number of patients have informed me that shortly before their present illness they had experienced symptoms such as general malaise, headache and backache, for which they had been treated as suffering from Influenza. On investigation, this proved to be of common occurrence, and generally applied to the milder and chronic cases.

In others, the slow onset of drowsiness, or of mild muscular twitchings leading slowly to the typical myoclonus, were the first distinguishing features. Diplopia generally occurs early in the course of the disease.

I have seen few cases where the onset was ushered in by vomiting; in fact, it has been my experience that vomiting is not a constant or important symptom.

It has been a common matter to be informed by parents that a child has shown increasing lethargy, taking/
taking no interest in companions or play, and going to sleep at meals or at the school-desk; and at night, instead of sleeping, walking about and muttering for hours.

In cases both of sudden and gradual onset, the mental state may provide the early prominent feature, confusional conditions, delirium or mania being present; or sudden intense headache, severe neuralgia and muscular pains may precede the development of further symptoms.

Those cases, in children, where the onset is similar to that of Sydenham's Chorea, are sometimes seen.

**GENERAL SYMPTOMS.**

**Fever:**

Some degree of temperature was practically always seen at some period in the course of the disease, and only in one or two cases was it absent throughout the whole stage. Its appearance does not necessarily coincide with the beginning of the illness, but may occur at any time; and a recurrence when recovery has apparently taken place is not uncommon.

While as a rule of no great duration, it may in some cases persist. I observed one case with an irregular/
irregular temperature for over four weeks.

It is not as a rule severe, but for a few days before death nearly always rises steadily.

(See appended charts)
Insomnia:

This was a very frequent and prominent symptom. It occurred particularly among the younger patients, and its treatment was a matter of great perplexity. Its frequent occurrence is now of great diagnostic importance.

Insomnia, occasionally accompanied by delirium by night, is generally found associated with lethargy by day. In some cases an almost complete reversal of habit takes place, and patients who were very drowsy by day hardly slept at all by night. Children were especially afflicted by this condition, and as in addition it forms one of the important sequelae of Encephalitis, it will later be considered under that heading.

Lethargy:

Among my cases in this epidemic, lethargy was generally absent, being confined to some of the more acute cases, where it was marked, and to those cases referred to above, where it was associated with nocturnal insomnia. These patients could be roused as a rule from their lethargic condition with no difficulty, and answers to questions were given with surprising accuracy, though sometimes there was some delay in replying. In cases where considerable constitutional/
constitutional disturbance was present the degree of lethargy was profound, and some time was required to awaken one of these patients, when the voice was never raised above a whisper in reply to questions.

The duration of this condition varies considerably. In my experience it passed in most cases when recovery from the acute stage set in, or when the temperature settled. In some, however, it persisted for a considerable time, and efforts of any kind to overcome this tendency were invariably useless. Two of my patients were distinctly lethargic for at least three months, and were discharged without any great improvement.

I have seen two cases of tumour of the frontal lobe where lethargy very similar to the drowsiness in Encephalitis was present. The cause, therefore, may be increased intra-cranial pressure; but I am inclined to think that in Encephalitis lethargy is due to some action on the nervous system by the virus of the disease itself, mainly owing to the fact of a more profound lethargy being present when a severe degree of toxemia evinced itself.

Headache:

Another important symptom was headache. It was quite early present, and in not a few persisted over/
over some time. Generally it was very severe, and bitterly complained of. Frontal and occipital headache were most prominent, but some cases complained also of pain over the vertex, and even in the back of the neck. Tenderness of the scalp was noted in one or two. Like other symptoms, this condition of headache was very resistant to treatment, and the ordinary analgesic drugs were in all cases useless.

SYSTEMIC SIGNS AND SYMPTOMS:

Respiratory System:

As a rule, no pathological conditions of this system were noted. In a few, early in the disease, a slight degree of Bronchitis was present; and in one case where diagnosis was never definitely established death was actually due to Lobar Pneumonia.

Disturbances of the respiratory mechanism and rhythm were both common and important; and while they were present in the acute stage, many remained, and are discussed as sequelae. A peculiar sobbing spasm characterised the beginning of one woman's illness, but quickly passed off.

Periods of polypnoea were seen in some cases, sometimes followed by apnoea; or periodic apnoea alone/
alone occurred. Hyperventilation was seen only in one or two.

Myoclonic contractions in many cases accompanied in close association these respiratory changes, in which the diaphragm was also concerned.

Respiratory habits, or tics, such as sniffing and blowing the hands persisted in children.

Cardiovascular System:

No changes that demanded particular observation were noticed, except in the heart rate. With regard to this, I have been forced to place some importance on remissions in the pulse-rate, or periodic Bradycardia.

In quite a number of cases a marked slowing of the pulse-rate, extending generally over several days, was seen at irregular intervals, as is exemplified by the chart below. As this occurred so frequently in patients either in bed or up and going about, it seems to be a feature of some importance.

In addition, the chart in Encephalitis very often resembles that in Typhoid Fever as regards temperature and pulse-rate. In many cases the similarity was quite marked where temperature of a moderate degree was present, as the pulse under that condition remained quite slow, and out of proportion to the degree of temperature present. (See Chart)

Charts appended/
Urinary System:

Albuminuria, as in other diseases, is commonly present during the febrile stage. It occurs, however, independently where there is no sign of any definite kidney lesion, at irregular intervals, and in the absence of temperature. It may, moreover, remain as a persistent condition. No alteration in the daily amount of urine was sufficient to attract notice. Incontinence and retention were present in moribund cases, and in some acute cases which recovered. The Di Katro reaction was distinctly positive in several cases.

Digestive System:

The tongue never showed any constant or typical appearance. In the early stages the tongue was often thickly coated with fur, and dry, sometimes accompanied by dryness and injection of the fauces. The mouth and teeth were sometimes in a dirty condition.

Herpes Labialis occurred in very few. Excessive salivation was an unpleasant feature in a few cases, but none appeared to persist to any great extent except in one young girl.

Dyspepsia occasionally presented some difficulty in patients who had never suffered from it before.
before. Pain was not complained of much, the common condition being a feeling of discomfort and a 'heavy feeling' with generally some relation to the taking of food. Careful attention to the mouth and teeth and strict dietetic measures were in some successful; but in others treatment had no effect in this condition, which was probably one of Nervous Dyspepsia.

Constipation in an extremely obstinate form was present in nearly every case. Vomiting seldom occurred.

**Skin:**

Disorders of the skin were limited to acute cases. One man, after a few days' illness developed a bright punctate rash, in some places macular in character. This persisted for several days before fading. There was no definite desquamation.

In another case of a girl of six years, the child was sent to hospital with a diagnosis of Scarlet Fever, and was found to have a bright punctate rash with folliculitis on the trunk. On the arms and buttocks was an irritative or pressure rash from the constant violent choreic movements.

Several of the acute cases developed violaceous spots. These were well-defined, circular areas of a faint violet colour, about the size of a sixpenny piece.
piece. They generally appeared on the skin of the abdomen, and faded slowly with recovery.

Severe perspiration was common, especially in cases tending to a fatal termination, and sometimes induced a folliculitis or transient erythema.

Herpes about the lips was seen in several. Trophic changes occurred only in those in a moribund condition; or in the severe uncontrollable myoclonic cases, in whom the constant restlessness and chafing produced trophic sores. The heels and malleoli were commonly affected, but sores were also found on the back of the head and over the buttocks. The feet also suffered, and one girl of a severe choreic type was found on admission to have one toe separating at the distal joint. It was a matter of great difficulty sometimes to prevent these happenings, and vigilant preventive treatment was very necessary.

Locomotory System:

Arthritis occurred in more than one case, but yielded easily to treatment.

Alterations in gait will be described later. Muscular wasting was in some cases of the myoclonic nature very severe, associated generally with distinct loss of subcutaneous fat.

The remaining symptoms form a great and important/
important group attributable, localizing or otherwise, to an affection of the Nervous System, and will now be considered together. The multiplicity of the lesions indicates a wide-spread effect upon the grey matter of the brain, particularly in the region of the mid-brain, the pons and the basal ganglia, and probably in some cases the spinal cord.

The nuclei of the cranial nerves are especially involved.

Ocular signs were prominent on account of their frequency.

Diplopia and Nystagmus were noted in nearly sixty per cent of the cases, and in some formed the only symptoms. The two were nearly always present together.

As a rule, Diplopia was early present, but in some occurred later in the course of the disease. Its actual determination was not always easy. The length of time it persisted varied considerably. Nystagmus occurred in practically the same number as as Diplopia, and varied a great deal in type. As a rule, the oscillatory movements were fine, but this was not always so. In a few, the 'ocular jerks' were very rapid and violent, not necessarily synchronous, the eyes oscillating at an incredible speed. Nystagmus only remained over a long period in a few.
Apart from these, any kind of disturbance of ocular movements may be present, not necessarily alone.

Partial or total loss of the power of convergence was not uncommon, either alone or in conjunction with other disorders.

Paralysis of accommodation was a common sign, and nearly always was bilateral, and very definite. Both tended to disappear shortly after their observation.

Of the third, fourth and sixth nerves, the third was far more commonly affected, and all three shared the extraordinary variation of the other lesions in Encephalitis.

It is not my intention to describe these paralyses in detail. They existed in every conceivable combination, and their temporary character varied considerably. It is necessary to mention that Ptosis may easily be overlooked, especially in the more profound lethargic cases. Actual changes in the pupils were seen. Inequality of the pupils was quite common, and irregularities in contour showed themselves in one or two. The light reflex was often sluggish: and two cases demonstrated the Argyll-Robertson pupil for several days. Hippus I noticed in one case.

Conjunctivitis was a common symptom. A bright pink injection of the conjunctivae was noted in most/
most of the acute cases, and was nearly always very marked just before death.

In addition to the ocular nerves, some of the remaining cranial nerves were affected, the commonest in my cases being a lesion of one or both seventh nerves.

Paralysis of the seventh nerve was surprisingly frequent. Facial diplegia was present in several, and weakness of one side of the face more common. As a rule, the condition slowly passed off.

Transient hemiparalysis of the Hypoglossal nerve was seen in a few cases.

The Trigeminal nerve was very seldom affected, and only one or two cases complained of neuralgic pains. Paralysis of the motor division was not seen.

Optic Nerve:

Frequent opthalmoscopic examinations failed to reveal any change in the optic nerve, except pallor of the disc in one or two. Hemianopia was never present in any of my cases.

Reflexes:

The condition of the reflexes varied a great deal. The knee-jerks were often exaggerated, and only in a few were they absent.

Absence of the abdominal reflexes in the acute stage, either on one or both sides, was of frequent occurrence.
occurrence, and possibly may be an important sign; while in others the reflexes were normal, or very brisk.

Babinski's sign and Kernig's sign were noted once or twice, but are not of diagnostic value.

As regards visceral reflexes, only in severe lethargic cases and in moribund patients did incontinence develop.

Myoclonus:

Clonic contractions of various muscles were seen in a great number of cases, and are of great value in diagnosis. The situation and degree varied within the widest limits. In some cases the contractions seemed to cause no discomfort, but others complained a great deal of pain. The patient may be entirely unaware that these spasms are taking place.

The upper part of the abdominal muscles frequently participated, a contraction on one side being followed by the other, or a synchronous movement taking place.

Almost any muscles in the body, however, seemed liable to be affected. More than one patient complained of pain and twitching in the back of the neck, or in the lumbar region. Contraction of the muscles of the thigh caused great annoyance in one case, and trophic sores on the heels and malleoli were a/
a consequence. In this case these contractions seemed to occur in rhythmic sequence with abdominal clonus. The accessory respiratory muscles also were affected in a few cases, and the contractions bore a very definite relationship in rhythm to respiration. In one man, a peculiar short grunt was produced at every respiratory act.

The contractions in some cases were not limited. Several cases showed continual clonus not only of the abdominal muscles, but of the arms, and muscles in other positions. The general impression was of a condition just lower in degree than the choreic types to be described. The movements are never necessarily rhythmic.

The movements in some cases, all children, resembled those in Chorea, and for that reason are termed Choreic and Choreo-athetotic. The resemblance to Chorea in one case was very marked, and considerable difficulty was experienced in establishing diagnosis. Grimacing, however, in this usual type was absent; and the purposeless movements, highly imitative of Chorea, tended after a time to develop into more or less rhythmic clonic contractions.

In other cases it would almost seem as if the whole muscular system contracted in segmental waves, and/
and a peculiar and constant writhing of the whole body was produced.

In one fatal case the most intense character was seen. The patient, a child aged six, very quickly became insensible. Irritative rashes and sores on the back of the head, the buttocks and the heels developed as a consequence of the violent movements. One moment the child lay still, and in the next few seconds the position changed rapidly from complete flexion to extreme opisthotonos. Rolling of the head, wild and uncontrollable threshing of the limbs, and the most grotesque grimaces completed this peculiar picture.

Katatonus:

It was only in the acute stages of illness that this feature occurred, and did not remain in the convalescent period.

Peripheral Neuritis:

Attention was early drawn to neuritis, and it is probably more frequent than may be imagined. Several patients complained a great deal of pain along the distribution of the nerves of the arm, and the condition in all was very persistent. It varied in intensity a great deal from day to day, and it also proved very resistant to all forms of treatment.

Epilepsy:

In/
In one case only the disease commenced with an attack of Jacksonian epilepsy lasting for twenty-four hours. In no other cases did I elicit a history of fits.

Blood:

Blood examinations revealed no frequent or important change.

Mental conditions:

Confusional conditions and hysteria were seen. Hallucinations were not common. Delirium as a rule was of the quiet muttering kind, but in a few the condition was very violent.

Other states form important sequelae, and will be considered under that heading.
TYPES OF DISEASE:

It is my intention here to describe shortly three types of the condition which attracted attention by reason of special features. This description is not intended as an attempt at classification.

I. CHOREIC.

One of the main points of interest in this small group was the extreme difficulty, in some cases, of differentiating from Sydenham's Chorea. The condition was seen in children. At the first onset the myoclonic movements closely resembled the quasi-purposive movements in Chorea, and the picture was complicated by lack of power, and spasms of the muscles around the mouth. As the disease progressed, however, the movements tended to become more and more rhythmic, associated with alteration of the respiratory rhythm, until true muscular clonus was present. The apparent grimacing was seen to be produced by clonic spasm of the facial muscles, and really consisted of a series of tics, a condition noted as a sequela of this disease. The speech was slow and deliberate, and some degree of temperature was usually present. The movements were not able to be controlled, and did not cease during sleep; in some cases, in fact, the violence was increased/
increased while sleeping. Psychical disturbances such as are seen sometimes in Chorea were absent in these cases.

It would appear that it is only in the early stages, when the movements are more intermittent, that mistakes in diagnosis are likely to be made.

II. LETHARGIC:

Not many cases of the acute lethargic type were seen, but the cases where profound lethargy was present evinced a high degree of virulence. It was curious, moreover, to find that these cases after a very severe illness generally made a good recovery, and presented a far more hopeful prognosis than many of the others.

The clinical picture when the disease was well established was very interesting. The lethargy was marked, and it was difficult to arouse the patient, who lay quite still in a practically comatose condition, taking no interest in the surroundings. Answers to questions were given after an appreciable delay in a husky whisper. The face was flushed, a moderate temperature was generally present, and some cases developed the violaceous spots on the skin already referred to. Incontinence was sometimes present. Feeding by the mouth/
mouth was difficult. In more than one case recovery was regarded as hopeless, yet improvement gradually set in.

One young girl lay in an absolutely comatose condition for days unable to swallow and insensitive to pain. The corneal reflex was absent. An intense conjunctivitis appeared, followed by hypopion ulcer in one eye. The child was expected to die at any moment, but she eventually made an excellent recovery, and was discharged quite well, with no apparent sequelae.

Muttering delirium and delusions were the usual mental accompaniments.

III. TYPHOIDAL GROUP:

Under this heading are included a few cases where the clinical or pathological findings suggested a peculiar resemblance or relation to Typhoid fever.

Attention was first drawn to this during the routine examination of the urine, when the Diazo reaction was found in some cases to be positive. The Diazo reaction was performed because of the noticeable clinical 'typhoidal' appearance of some of the patients. The facies was in some very similar to that in Enteric fever; while the chart suggested a protracted illness from that disease. This latter peculiarity has been described under the Circulatory System.
In those cases where the Diazo reaction was very strikingly positive, an agglutination test with a standard Typhoid emulsion was done, but in all proved negative.

In two cases, however, the Widal reaction was positive up to a dilution of 1 in 250 where the Diazo reaction was negative.

This small group included seven fatal cases, in all of whom post-mortem examination was carried out; and four showed some degree of ulceration or congestion of the Peyer's patches and solitary glands of the intestine, and one of the four had had a positive Widal during the acute stage of his illness.

The pathological result was shown mainly in the large intestine, where, in each case, there was definite congestion and also ulceration of the solitary glands. In one case, however, the lower end of the small bowel shared in the process, and there was a definite ulcer of one of the Peyer's patches. In no case was the spleen enlarged, but in one there was enlargement of the mesenteric glands. I have had the opportunity of examining cut sections of the brain in two of these cases, and the typical appearances of Encephalitis was found.

From one of these cases and from three others where/
where there was no ulceration, a bacillus was isolated post-mortem from the spleen and gall-bladder, morphologically resembling the B. typhosus. In each case the bacillus was motile.

The following were the characteristics of these four cases during life:

**Case I.** Widal positive — Diazo negative — no ulceration post-mortem of bowel.

**Case II.** Widal not done — Diazo negative — no ulceration.

**Case III.** Widal positive — Diazo negative — Definite ulceration post-mortem.

**Case IV.** Widal and Diazo not done — No ulceration.

By the courtesy of Professor Douglas and Dr. Simson of the Pathological Department, Sheffield University, I am able to reproduce below the results of the sugar tests and agglutination of the organisms isolated post-mortem in these four cases from the spleen and gall-bladder. The numbers of the cases correspond. The sugar tests were identical with Typhoid except (Cases II. and III.) with Indol; while there was no agglutination except in Case I.

The organism in each case was a motile, Gram-negative bacillus.
<table>
<thead>
<tr>
<th></th>
<th>Case I</th>
<th>Case II</th>
<th>Case III</th>
<th>Case IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Glucose</td>
<td>Acid</td>
<td>Acid</td>
<td>Acid</td>
<td>Acid</td>
</tr>
<tr>
<td>Mannite</td>
<td>Acid</td>
<td>Acid</td>
<td>Acid</td>
<td>Acid</td>
</tr>
<tr>
<td>Maltose</td>
<td>Acid</td>
<td>Acid</td>
<td>Acid</td>
<td>Acid</td>
</tr>
<tr>
<td>Saccharose</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Gelatine</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Milk</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
</tbody>
</table>

In addition to these rather bewildering findings, attention was drawn to the possible susceptibility of patients suffering from Encephalitis to Enteric fever. Two cases, both typical examples of Parkinsonism, later developed Typhoid, one while in hospital, and the other within twelve days of discharge.

It is interesting to note with regard to the negative agglutination from three of these cases, that the same result was obtained with organisms isolated from the spleen of a fatal case of Typhoid in this hospital in December, 1924.

The sugar tests were those of Typhoid, and the
the organism was morphologically identical, but there was no agglutination.

**DIFFERENTIAL DIAGNOSIS**

As a rule the existence of the disease was easy enough to recognise, and only in a few cases was it difficult to establish an accurate diagnosis.

Nearly one third of the cases admitted to this hospital with a diagnosis of Epidemic Encephalitis were found to be suffering from other conditions of a wide and varied nature.

Of the doubtful cases the greatest trouble was encountered with the patient in a moribund condition. Two cases of this nature deserve special mention, where the cause of death was revealed by post-mortem examination. In one, death was found to be due to Uraemia, and the other, that rare condition, Pachymeningitis Interna Haemorrhagica.

The apparent resemblances of Chorea and Enteric fever have already been discussed. Disseminated Sclerosis has sometimes to be eliminated. One fatal case with a Scarlatiniform rash was notified as suffering from Scarlet fever.

The commonest mistake made in young children was over the condition of Tubercular Meningitis.

Six/
Six of these cases, all fatal, were notified as Encephalitis. I have referred before to this fact, and would again emphasize the necessity of eliminating this disease in young children. There is no doubt, however, that the similarity may be very close.

Three cases of hemiplegia were discovered. Among the other cases wrongly notified as Encephalitis was a variety of diseases, including Cerebro-Spinal Fever, Chicken-Pox, Pneumonia, and Acute Mastoiditis.

There is no doubt that mild cases may occur, and as these are just as liable to produce sequelæ, it is important to endeavour to recognise them.

It may be very difficult to distinguish Encephalitis from tumour of the frontal lobe. I have formerly seen one case diagnosed as lethargic Encephalitis, where post-mortem a small tumour of the right frontal lobe was found; and among this series I had one case that presented considerable difficulty in differentiation.

Cases in the early stages may be very difficult to recognise.

**PROGNOSIS**

The immediate prognosis as regards life and death may be difficult or impossible, especially in the/
the lethargic cases. The mode of onset is no guide, nor is severity of attack, except where constitutional symptoms are very severe.

A gradually rising temperature usually occurs in the days before death, and is therefore a bad sign. Incontinence is not necessarily a bad feature, but is serious if occurring in conjunction with rising temperature and increasing lethargy, and will probably then indicate a fatal end. Profuse sweating is generally associated with these signs.

Of the fatal cases, with one exception, death took place within about three weeks or a month of illness, so that it would seem that a lengthy illness does not indicate a fatal ending, which, in fact, was the case.

The degree of lethargy itself is of no help, except under the conditions stated above. Myoclonic cases did not seem to be of grave import.

As to other things, prognosis is necessarily difficult, owing to the short space of time which has elapsed. As regards sequelae, severity of disease has proved to be of no significance. Some of the very acute cases appeared to have recovered completely, and important sequelae resulted after quite mild types of infection.
At least twenty cases left hospital with some degree of Parkinsonism, and these cases had been of all types, but generally of the lethargic and myoclonic nature.

Mental changes were not uncommon, and insomnia was a problem which seemed best dealt with by institutional treatment.

Myoclonus tended generally to become less and less severe with time. Ultimate prognosis is of course impossible.
In the main it must be confessed that the treatment of this disease has given very disappointing results. It would appear that certain symptoms are very resistant to any form of treatment, entailing a great deal of discomfort on the part of the patients. The more important will be first dealt with.

**INSOMNIA:**

The treatment of insomnia, especially in the children in whose cases it seemed to be a more troublesome feature, presented a difficult problem. It commonly occurred in association with drowsiness by day, while with the wakefulness at night there was generally an exaggeration of the usual respiratory and motor signs, sometimes with delirium.

The ordinary hypnotic drugs were soon found to be ineffectual except in overwhelming doses, and the more powerful narcotic agents were for obvious reasons avoided.

As the nocturnal excitement was the source of a great amount of trouble, various means were tried to induce sleep, and some success was gained by the use of boiled milk. This was tried twice in three cases of/
of young children, the alternate nights an equal quantity of sterile water being given. The boiled milk and the sterile water were given in doses of 2 c.c. intramuscularly at 7 o'clock in the evening in each case.

The following table indicates the results obtained. None of these cases had slept on an average more than a few hours a night for weeks.

<table>
<thead>
<tr>
<th></th>
<th>Case I</th>
<th>Case II</th>
<th>Case III</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st. night Boiled Milk 2 c.c.</td>
<td>Slept 8 hrs.</td>
<td>Slept 8 hrs.</td>
<td>Slept 8 hrs.</td>
</tr>
<tr>
<td>3rd night Boiled Milk 2 c.c.</td>
<td>Slept 8 hrs.</td>
<td>Slept 8 hrs. 30 mins.</td>
<td>Slept 7 hrs.</td>
</tr>
<tr>
<td>4th night Sterile water 2 c.c.</td>
<td>Slept 3 hrs. 45 mins.</td>
<td>Slept 10 hrs.</td>
<td>Slept 4 hours</td>
</tr>
</tbody>
</table>

The injections were not followed by any local or general disturbance. The results would seem to indicate that the injections of boiled milk were successful.
successful in inducing sleep, and that further investigations in this direction might be useful.

It was noted that in the case of those patients suffering from insomnia who had been under observation for some time, the condition improved more and more as time went on, until most could be depended on to have seven or eight hours natural sleep every night. This result was almost certainly due to the effect of firm institutional treatment. With adults, however, there was no great success; and in these patients, the actual enforcing of exercise and occupation of the mind by day never assured sound sleep. The tactful interesting of children in some occupation, and general kindly handling are measures that are very helpful in dealing with this particular symptom.

MYOCLONUS:

Many cases that exhibited myoclonus did not seem to be much inconvenienced thereby, or merely felt a wave of mild 'twitchings' now and then. There were some, however, to whom the constant clonic contractions were a source of a great deal of pain and considerable mental worry. When the muscles of the legs were affected there was always, in addition, the liability of the production of trophic sores. The abdominal contractions were associated sometimes with respiratory spasm.
spasm, expiration being of an explosive, grunting nature.

Many drugs were given an exhaustive trial, including the Bromides, Chloral, Chloratone, Dial, and others of a similar nature. Hyoscine was also given, but, in common with the rest, proved a complete failure. No improvement, from my observations, could be ascribed to any of these drugs. It was found impossible to try the effect of auto-therapy.

The reassuring feature of this condition was that in time it tended to quieten down considerably or to disappear altogether, especially as the general condition began to improve.

In the milder cases, improvement was quickly produced by the use of re-educative exercises and 'hand and eye training'. Though these exercises did not necessarily abolish the clonus, they certainly effected the co-ordinated performance of the finer movements, and helped to lessen the often accompanying tremor.

I had only one case which left hospital with still obvious clonus -- in the remainder it had entirely disappeared, or was so slight as to cause no inconvenience. One quite severe case which I saw six months after discharge had only the very finest contractions/
contractions in one arm.

General treatment and proper supervision would again seem to be invaluable in this condition.

HEADACHE:

Headache, which by its persistence so often added to a patient's misery, was very resistant to any ordinary form of treatment. The drugs of the antipyretic group were found useless. Lumbar puncture is not to be recommended.

NEURITIS:

The experience with the treatment of headache was renewed in a few cases of Peripheral Neuritis. Treatment of any kind was unavailing.

GENERAL TREATMENT:

It is well for even mild cases to be put to bed and watched for some time.

With every acute case careful nursing is necessary. Careful attention to the skin is required to prevent the formation of bed-sores; and violent choreic cases must be prevented from producing injury by unconscious self-infliction. While there is temperature, tepid sponging may be found very useful.

The toilet of the mouth and tongue should be carefully observed. As a measure of prevention of dissemination/
dissemination of the disease, spraying of the nasopharynx with a dilute solution of potassium permanganate should be done daily. The infectivity, however, except in a few cases, is probably very low.

In view of the tendency to severe constipation, a daily evacuation of the bowels is desirable.

No patient should be allowed to get up too soon -- convalescence should be well established. Open-air treatment, when possible, should be allowed.

The diet given is that similar to diet given in any acute febrile condition. As a rule, no difficulty is experienced in feeding these patients.

Drugs:

Several drugs have already been referred to. I have found no drug to be in any way a specific for this disease. Hexamine was early used and, after a long and exhaustive trial, was abandoned. The administration of Chloroform gave no results. Vaccine treatment and serum-therapy were not tried.

In convalescence, tonics such as Iron and Arsenic may be given.

Lumbar puncture was only done for diagnostic purposes, and its frequent performance, in my opinion, is not desirable.
SEQUELAE or AFTER-EFFECTS

These names are hardly applicable, inasmuch as some of the remaining signs may appear during the course of the illness as quite important symptoms, and Parkinsonism may be early seen. There appears to be no definite time at which any remaining effect is likely to first evince itself. I have had no opportunity of observing any very late sequela.

MENTAL CHANGES:

The mental changes are important, especially in young children, in whom indeed, change of character may be the first sign of the disease. As a rule it is not long before the first symptoms of mental instability occur.

It was my experience, in children, that it was practically only among those suffering from insomnìa that mental change was prominent.

A complete change in character in some cases seemed to be brought about, and while these children were aware that their behaviour was wrong, they seemed quite unable to correct themselves.

While some of their acts were quite petty, and indeed ridiculous, they were liable to become at any moment more serious.

One or two in a short space of time became the/
the most accomplished and glib liars, and quarrelsome-ness was common almost to all. One boy persistently refused food for two or three days over some fancied slight.

Though often sullen and very cunning, there yet seemed to remain a certain sense of humour, as though all the better nature had not disappeared. Destructiveness and disobedience were common. An extraordinary mingling of tact and authority is evidently necessary to control these children, and it is quite imaginable that they are beyond parental control as a rule.

In one or two more serious aspects began to appear; sometimes assaults upon fellow-patients took place. Rudeness and attacks little short of violence upon the nurses had to be dealt with.

One boy was discovered endeavouring to choke himself one night with a piece of tape, though apart from this, any suicidal tendency was not noted in any other.

Nocturnal excitement was common, with an exacerbation of any marked habits. Shouting and screaming at night time, by which the other patients were kept awake, was a troublesome factor.

There seems no doubt that institutional treatment over some time is necessary for the majority of/
of these children; and while their habits can be well subdued in hospital, it can easily be imagined what would happen if they were let loose without proper supervision.

In adults, excitement and rowdiness were not noticeable, though insomnia was common. Depression was seen occasionally, and this amounted to a marked melancholic state in one man. Though delusions were uncommon, one man was suspicious for days about his food, which he said was poisoned, and would not touch it. An air of suspicion was present about some of the men, which was hard to combat.

It must be remembered that any are liable to loss of control at any time, from which tragic occurrences may result. One woman, who left hospital apparently well, shortly afterwards assaulted her husband and succeeded in gashing his throat with a knife.

The number of certifiable cases does not seem to be great, and I have only heard of one of my cases who has been sent to an asylum.

Confusional states occurred during the acute illness, but violent delirium was not common.

RESPIRATORY:

Only one case showed evidence of remaining alteration of respiratory rhythm. In this young man there/
there was definite irregularity of breathing, with periods of hyperpnoea.

Respiratory tics were seen in one or two. Continual blowing on the hands and loud sniffing were persisted in by a boy, in whom these habits were exaggerated at night. I have seen another case where a loud sniff was produced by pressing the finger on one nostril and sniffing with the other. These habits seem to be controllable, but are easily resumed.

Another case, a little girl, developed an explosive cough which she seemed to delight in producing.

A patient in the same ward had a very troublesome cough due to Laryngitis, and I am inclined to think that in this example the explosive cough of this child was first produced on account of the imitative powers, of which some of these patients became possessed, and was afterwards persisted in.

PARALYSES:

Paralyses of any sort were uncommon. I have recently seen one patient who still has a certain degree of facial hemi-paralysis. I have not seen squint persist.

Pare nyctagmus may persist for a long time; as also may loss of accommodation.

MYOCLONUS/
MYOCLONUS:

As I have already stated, this, in my experience, tends to disappear. It may remain, however, separately, or in conjunction with other signs, or associated with the Parkinsonian syndrome.

It is seen as a series of fine, rapid movements; or as irregular, asynchronous contractions. Choreic movements may also be seen. In addition, tremors of a fine nature, especially when associated with Parkinsonism, remained in several.

One man still has a marked tic producing spasmodic contractions of the muscles of the lips and the face.

PARKINSONISM:

About twenty patients on leaving hospital could be said to have some degree of this feature.

The development occurred at almost any period of the disease, several during the acute stage, and others much later in convalescence. The actual condition of Parkinsonism was complicated in most by other signs; residual paralyses; myoclonus, or respiratory habits. In one or two there was distinct mental change, a condition seen in one woman who was pregnant.

The development of the facies and general appearance...
appearance may be very quick, while in others a considerable period of time elapsed.

All ages were represented, the worst case I saw occurring in a girl aged ten.

The accompanying tremor was in all very fine, but there was always some degree of rigidity. Loss of power and loss of co-ordination were also noted. The gait tends to become typical.

The progress of this condition may be almost arrested, or the extreme results may appear very quickly.

In the case of the young girl referred to above, at the time of discharge there was quite definite Parkinsonism, with fine tremor. The child, however, walked quite well. She was well behaved. When I saw her two months later there was an extraordinary change owing to the rapid progress of the condition. Walking was difficult and slow, the back pronouncedly bent. There was a typical mask-like face with constant salivation. Tremor was still present.

The knee-jerks were exaggerated. Associated with a loss of her former brightness and mental capacity, there had arisen a tendency to disobedience and wickedness, and she was beginning to prove troublesome.
The whole formed a very tragic picture.

Of the few men whom I have been able to follow up, the condition does not seem to have advanced markedly.

**PATHOLOGY**

**CEREBRO-SPINAL FLUID:**

No important definite changes were found in the examination of the cerebro-spinal fluid.

The fluid was generally at normal pressure, or under slightly increased pressure - clear, and colourless.

The globulin content varied from nil to slight excess. The cell-count was generally distinctly higher than the normal.

Sugar reduction was always obtained.

The Wassermann reaction was negative in each case; and all cultures remained sterile.

The colloidal gold curves varied considerably in each case, and none resembled those of the Luetic or Paretic type.

Various specimens of faeces were sent to the Pathological Department of Sheffield University for examination, but no results were obtained. Washings from the naso-pharynx similarly proved negative.

**BRAIN:**
BRAIN:

Of the fatal cases, post-mortem examination was performed in all except one. The naked-eye appearances were practically insignificant as regards the brain and meninges. The changes in the bowel have been referred to under the Typhoidal group. The meninges as a rule showed little more than congestion of the blood-vessels; but in one or two cases small haemorrhages were seen.

The brain, in several cases, showed quite definite flattening of the convolutions; and, on section, similar congestive appearances, mainly in the grey matter, with small haemorrhages. In one case, there was marked oedema of the brain.

Haemorrhages elsewhere were seldom found. In one case, sudden death took place, obviously due to internal haemorrhage. At post-mortem examination, a large retro-peritoneal haemorrhage was found, the origin of which could not be traced. The spleen was enlarged and hyperplastic. The diagnosis in this case was doubtful, and I am unable to say whether or not this was an example of haemorrhagic Encephalitis.

The microscopic appearances in the brain are now well known, and the sections I was able to examine showed the usual pathological results.

The obvious and striking feature was the presence/
presence in the brain substance of small mono-nuclear cells, particularly grouped in a concentric manner around the blood vessels. In these cases, this change was only found in the basal nuclei and the medulla. The extent is very variable. The rings of closely-packed cells around the vessels ranged up to three or four; and entirely surrounded the vessel, so that the appearance showed whether the vessel had been cut obliquely or straight across.

In the one case where this feature was the most striking, death had taken place from Chronic Nephritis and Uraemia. There had been considerable doubt as to the diagnosis of Encephalitis in this case, and the result was interesting as showing that the pathological lesions typical of Encephalitis may be seen in other diseases.

For permission to reproduce the above findings, and to examine prepared sections, I have to express my great indebtedness to Professor Douglas and Dr. Simson, of the Pathological Department, Sheffield University. The statements refer only to my own cases.