MENINGITIS DUE TO PYOGENIC ORGANISMS.

A Discussion on Cases Occurring in Infectious Diseases Hospital Practice.

by

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This paper deals with Meningitis due to pyogenic organisms, including the pneumococcus, Haemophilus influenzae, streptococci and various other organisms of the order Eubacteriales other than the meningococcus (Neisseria intracellularis) and tubercle bacillus (Mycobacterium tuberculosis). It is based primarily on an analysis of cases appearing in the records of the Edinburgh City Hospital for Infectious Diseases during the years 1916 - 1946, and on cases seen personally at Rush Green Hospital, Romford, during 1946 - 1948.

Meningitis due to organisms of other orders and the so called Serous Meningitis are also excluded. This group includes Meningitis due to viruses, spirochaetes, yeasts and fungi, and the C.S.F. reaction which occurs in various acute infections whether general or in close proximity to the C.S.F. spaces.

The effects of the changes in treatment of pyogenic meningitis which have taken place during
the past eighteen years is discussed, and the increasing necessity for early and accurate recognition of the various types of the disease is stressed.

Some of the difficulties of diagnosis of the different pyogenic meningitides are considered, together with the precautions to be observed in the prevention of avoidable meningitis.

My grateful thanks are due to Dr. A. Joe, Medical Superintendent of Edinburgh City Hospital for Infectious Diseases, for permission to use the hospital records, and to Dr. E. James, Medical Superintendent of Rush Green Hospital, Romford, for permission to quote cases seen there.
INTRODUCTION

In addition to the marked improvement in recovery rates and rapidity of cure of meningoococcal meningitis consequent upon the introduction of the sulphonamide group of chemotherapeutic agents, there has been an improvement, although not a corresponding improvement, in the prognosis of cases of meningitis due to various other pyogenic organisms. The antibiotics are now also playing their part in making it possible to offer at least a hope of recovery where formerly there was almost none.

It was with a view to examining the changes in treatment and the results to be expected that an investigation was made into the records of cases admitted to Edinburgh City Hospital for Infectious Diseases.

Prior to 1930 the case notes were not available, but the admission books gave a certain amount of clinical information about the cases. These books were therefore scrutinised as far back as 1916, as it was felt that the information therein might in some degree extend and amplify that gleaned from the later
clinical notes. With a few exceptions the cases fall into chronological groups as follows:

1. 1916 - 1929 inclusive - Case Notes not available.
2. 1930 - 1937 inclusive - Pre-sulphonamide period.
3. 1930 - September 1944 - Sulphonamide period.
4. Oct. 1944 - March 1946 - Penicillin period (with or without sulphonamides).

In the case of Meningitis due to Haemophilus Influenzae the division between the pre-sulphonamide and sulphonamide periods must be postponed until the end of 1940, and this must be borne in mind when the different periods are discussed.

Overall Picture

During the whole period of thirty years ending 31st March 1946 a total of 142 cases of Pyogenic Meningitis were admitted to Edinburgh City Hospital. In addition to this number there were a further twelve cases which from the circumstantial evidence were almost certainly pyogenic meningitis, but in the absence of definite evidence these have been excluded from the figures. A group of about seventy cases recorded as "Non-specific meningitis" have also been excluded, it being apparent from the case records that
the vast majority of these were almost certainly meningococcal meningitis in which the meningococcus was, for one reason or another, not found.

Of the 142 cases, 99 (69.8%) were Pneumococcal, 25 (17.6%) due to Haemophilus Influenzae, 14 (9.8%) Streptococcal, and the remaining 4 (2.8%) were due to other organisms, namely Staphylococcus, Pneumobacillus of Friedländer, Salmonella Dublin, and Bacillus Coli.

Fifteen (10.6%) of the 142 cases recovered. Of these, 10 (66.7%) were pneumococcal, 4 (26.7%) due to haemophilus influenzae, and the remaining one streptococcal.

The annual incidence is set out in Appendix 1.

Considering the overall figures in relation to the periods mentioned on page 2, 46 cases occurred in the "pre-record period" and 24 cases in the "pre-sulphonamide period". All 70 cases were fatal.

Of the 57 cases occurring in the "sulphonamide period" 9 (15.8%) recovered.

During the "Penicillin period" 15 cases occurred, of which 6 (40%) recovered.

These figures appear in tabular form in Appendix 2.
More detailed consideration of these figures and the relevant case records is best carried out by grouping the cases according to the infecting organism and examining each group in turn, for, although the symptomatology may be similar, there will become apparent certain differences in behaviour among the several types of pyogenic meningitis.
PNEUMOCOCCAL MENINGITIS

During the thirty year period ending 31st March 1946 ninety-nine cases of pneumococcal meningitis were treated at Edinburgh City Hospital.

ANNUAL INCIDENCE

The average annual case incidence of 3.3 is exceeded during two periods, first during the latter years of the 1914 - 1918 War, when for the years 1916 to 1919 inclusive the average annual number of cases was 5.25. The second occasion was during the late war when for the years 1940 to 1944 inclusive the average annual incidence was 8.6, the maximum figures being 13 cases during 1940 and 1941.

(Appendices 1 and 4)

SEASONAL INCIDENCE

The incidence by months is set out graphically in Appendix 4 from which it can be seen that the incidence is markedly above the average (3.25) in March (14), while the figures towards the end of the year fluctuate between six and eleven.

AGE DISTRIBUTION

The ages of the patients ranged from seven weeks to sixty-seven years. Fourteen of the cases were infants under twelve months of age. More than half
the total (51.5%) occurred in children in the first
decade of life, and 16.2% in the second decade. Then
follows a drop to three (3%) in the third decade,
while the remainder are fairly evenly distributed
throughout the next four decades.

The age distribution is shown graphically in
Appendix 4.

SEX DISTRIBUTION

There is a well marked preponderance of males
among the cases, sixty-four (64.6%) being males and
thirty-five (35.4%) females.

The disproportion is most marked under the age of
one year (thirteen males and two females) but is
evident throughout the age groups with the exception
of the third decade (one male and two females)

(See Appendix 4)

During the period 1930 to 31st March 1946 the
fifty-eight cases were made up of forty males (69%) and
eighteen females (31%)

CLINICAL FEATURES

In the absence of full clinical records before
1930 the earlier cases are excluded from consideration
in this and the following sections.
PRESumptive primary focus

In approximately half the cases the history does not record any significant illness or injury immediately preceding the onset of meningitis.

On the other hand, although proof is in most cases lacking, there is some suggestive circumstantial evidence as to the primary focus in other cases. Six cases give a history of head injury before the onset of meningeal symptoms.

Case 11, a boy of eight years, fell off a desk and struck his head (behind the right ear) against a metal rail some days before the onset of meningitis. He lost consciousness for a short time but showed no other signs of serious injury except occasional vomiting for several days.

Case 16, a boy of five years of age, fell and struck his head two days before onset. He may have been unconscious for a short time. He had a blood-stained, watery discharge from the nose (presumably cerebrospinal fluid).

Case 19, a boy of thirteen years, knocked into another boy two days before onset of meningitic symptoms, and received a bruise on the right temple. He had, in addition, a history of fractured skull four years previously.

Case 23, a male infant aged nine months, was struck on the head three days previously.

Case 35, a boy of six years, bruised the back of his head two days before onset. This boy had at the time a purulent nasal discharge. He also had a history of fractured skull one year previously.

Case 56 was a Polish soldier who was still suffering from gunshot wounds of the head, and is the only case in the series where there was a frank penetrating wound affecting the cranium.
In cases 11, 19, 23 and 35 the injury does not appear to have been severe.

In six cases there is a history of earache. In three of these there was definite otorrhoea. One of the remaining three had at the same time a severe cold and frontal sinusitis.

None of the cases is reported as suffering from mastoiditis.

In case 12 there is a history of epistaxis, following which the nose was packed for eleven days, until two days before onset of meningitis.

Eleven cases give a history of some respiratory tract infection, including five cases of broncho-pneumonia and one empyema. In the remainder there was at least bronchitis and possibly pneumonia.

Case 39, a male infant aged fifteen months, had been vaccinated twelve days previous to onset.

Case 15, a woman aged 23 years, three days before the onset of meningeal symptoms had an abdominal operation at which her appendix was removed. She was found to have an acute salpingitis.

In case 9, a man of 59 years, there was a history of shivering and headache two days before admission. Pain in the right upper abdomen with enlargement of the liver and slight jaundice became apparent on the following day. Pain in the neck and along the spine developed on the day of admission.

In five cases lumbar puncture was performed before admission and meningococci were reported to be present. Whether the organisms were identified by a
bacteriologist is not clear from the notes, but in two cases the clinical response to treatment was good at first, and a rapidly fatal relapse occurred after a period of clinical improvement, pneumococci being found in the C.S.F. during the relapse. (Cases 17 and 27).

MODE OF ONSET

Apart from the various precursors detailed in the previous paragraphs, the histories of onset of the actual meningitis reveal a number of predominant common factors.

Headache

Headache is the commonest initial symptom and appears in the history of thirty of the cases. Of the remaining twenty-eight, thirteen were under eighteen months of age and thus unable to express themselves. The remainder were either delirious or semiconscious on admission, and unable to give a good history. The character and location of the headache is in most cases not recorded, but several patients are reported to have had occipital headache.

Shivering or Malaise

Shivering or malaise indicating the onset of pyrexia was commonly associated with the initial headache.
Vomiting

Vomiting is reported in thirty cases. The vomiting is not confined to children but is distributed throughout the age groups.

It commonly appeared some hours after the onset of headache.

Constipation

The presence or absence of this symptom is not recorded in a sufficient number of cases to be worthy of analysis.

Disturbances of Consciousness

One or more of the terms "Drowsy", "Semicomatose", "Comatose" or "Unconscious" occurs in almost every case, the time of onset of these signs varying from a few hours to a few days of onset of the disease.

In five of the cases convulsions were reported. Of these, three were infants and one a boy of eight. The remaining case was the soldier, already mentioned, who was suffering from a penetrating wound of the cranium, so that it is difficult to say whether the convulsions were primarily due to the wound or to the meningitis.

In addition to those symptoms which are referable to the meningitis, the cases naturally presented other
symptoms due to the primary disease where such was present.

The onset of these symptoms was, on the whole, fairly rapid, although usually lacking the dramatic suddenness of onset found in subarachnoid haemorrhage or other cerebral vascular accidents. One patient, however, (Case 5), a boy of ten years, complained of headache at 12.30 p.m. one day, vomited at 1 p.m. and became comatose by 3 p.m.

The majority of the cases passed through these stages at a much slower rate, so that the stage of coma was not reached for two or three days.

CLINICAL FEATURES ON ADMISSION TO HOSPITAL

Day of Disease

The majority of the cases were admitted on the second or third day of disease. To be precise, four were admitted on the day of onset, nineteen on the following day, fourteen on the third day, eight on the fourth, two on the fifth. The average in these cases is third day. In the remaining eleven cases the history is not clear or is confused by the pre-existence of another condition. (Cases 1, 2, 6, 11, 17, 18, 27, 29, 30, 41, 42.)
Temperature

All cases had elevated temperature at some stage in the disease, but seven of the cases had "normal" or subnormal temperature on admission. The maximum admission temperature was 104.4°F (Case 8), and the average was fractionally under 101°F.

Pulse Rate

The pulse rate was in most cases considerably raised, but in one third of the cases shows no great increase.

In view of the differences in age groups and the range of normal pulse rates, a detailed analysis would serve no useful purpose.

Respiratory Rate

The respiratory rate showed no gross abnormality except in cases where there was a co-existing respiratory condition.

General Condition and Mental State

This naturally varied considerably, depending upon the stage of disease and the age of the patient. Typically the patient was drowsy or semiconscious, but irritable when roused. One in four of the patients was delirious on admission. Photophobia was remarked on in four cases.
SIGNS OF INCREASED INTRACRANIAL PRESSURE OR IRRITATION.

Neck Rigidity

Of forty-nine cases in which this sign is mentioned it was absent in four cases (one adult and three infants), slight in four, "present" without qualification in twenty-six cases, and marked in the remaining sixteen cases.

Head Retraction

Head retraction was present in eighteen cases and marked in ten of these. There was no preponderance in any age group.

Opisthotonus

Five of the patients were in a state of opisthotonus on admission. The ages of the patients were seven weeks, three and a half years, six, eight and thirty-four years.

Bulging Fontanelle

Of the eight cases under one year of age, bulging of the anterior fontanelle is recorded in three. The sign was also present in a child of eighteen months.

Kernig's Sign

Kernig's sign was negative in nine cases. In thirty-four cases it was definitely positive and in eight of these, strongly so. In the remaining seven cases the sign was weakly positive or doubtful, or not specifically mentioned.
SIGNS OF INTERFERENCE WITH NERVE PATHWAYS

Tendon Reflexes

The knee jerk response varies from absence to exaggeration.

It was absent in six cases, sluggish in a further six, and exaggerated in ten, including one case in which clonus was elicited.

Ankle clonus was elicited in one other case and where recorded the ankle jerk parallels the knee jerk.

Superficial Reflexes

Abdominal Reflexes. The abdominal reflexes were present in ten cases, absent in twenty-one cases and doubtful or unrecorded in the remaining twenty-seven cases. The reflex was thus negative in approximately 60% of cases in which there is a definite record.

Plantar Reflexes. These are recorded in twenty-six cases, in four of which the response was extensor. In each of these four the abdominal reflexes were absent and the patient very ill.

Urinary Retention

Retention is recorded in the notes of seven cases. Two of these were females aged five and forty-four years. The remainder were males, aged nine, thirteen, forty-six, forty-eight and sixty-seven years. (i.e. on the whole the older cases.)
Eye Signs

Strabismus occurred in six cases, the nature and extent varying.
Ptosis was present in two cases, one of which is associated with strabismus.
Nystagmus was noted in two cases.
Pupils. The pupils varied in size, being dilated in some cases and contracted in others. In three patients the pupils were unequal. In the majority of cases the pupils reacted normally to light, but a few cases showed a sluggish reaction.

Other Nervous Signs

Various other signs of irritation or interruption of nerve pathways appear in a few of the cases.

In Cases 5, 30, 33 and 40 muscular twitching is recorded, while case 33, an infant aged seven months, also exhibited conjugate deviation of head and eyes upwards and to the left. Later, following lumbar puncture, the child's breathing stopped but started again following ventricular puncture.

Cases 4 and 18 suffered from carpopedal spasm. The former gave a history of anuria, while the latter had been vomiting periodically for six days.
CEREBROSPINAL FLUID FINDINGS

Number of Lumbar Punctures

In all one hundred and forty-four lumbar punctures, three cisternal punctures and one ventricular puncture were carried out. In the early years, second and later punctures, in the few patients who survived long enough, were carried out for the introduction of serum. During the sulphonamide period this was discontinued but has since been resumed for the intrathecal introduction of penicillin.

The physical characteristics of the fluid naturally depend on various factors, including the stage of disease in relation to onset and treatment.

The initial lumbar punctures will be considered first, and the paragraphs which follow do not refer to cerebrospinal fluid obtained after treatment is commenced, unless otherwise stated.

On the average, the first lumbar puncture including those performed before admission, was performed on the third day.

The patients who recovered did not have their first lumbar puncture appreciably earlier than those who died.
Pressure

A manometer was used only in five cases; in one of these the reading was 200 mm C.S.F., while in the remainder the pressure was over 300 mm C.S.F. In the great majority of cases the pressure is recorded as greatly increased. In cases 13, 15, 35, 41, 52, 54 and 57 it is noted as "low", "normal" or "slightly increased".

Appearance

The turbidity varied from almost clear to thick purulent, by far the commonest description being "turbid". To be precise, nine were almost clear or hazy, five opalescent or slightly turbid, thirty-one turbid, and five thick.

The presence or absence of clot formation is not adequately recorded for detailed analysis, but the presence of either clot or fibrin flakes was common.

Colour

The colour is recorded only in twenty of the first or second lumbar punctures, many of which were done pre-admission. Of these fifteen are mentioned as being whitish or greyish, and the remaining five as yellowish, greenish or greenish-yellow.
On standing the deposit was either purulent or granular.

**Cells.**

Cell counts were not done in detail (except in two cases in which the counts were 200 and 6,800 cells), but the predominant type of cell was with few exceptions polymorphonuclear. Lymphocytes appear in fair numbers in a few cases and predominate in one, Case 13, a second day case in which the fluid contained large numbers of pneumococci.

**Chemistry.**

In a small proportion of cases the cerebrospinal fluid protein, sugar and chlorides were estimated.

**Protein.** The protein content varied from 45 to 1120 mgm per 100 c.c. of C.S.F., the average being 511 mgm per 100 c.c.

**Sugar.** C.S.F. glucose ranged from nil to 64 mgm per 100 c.c. and averaged 13.5 mgm per 100 c.c.

**Chlorides.** C.S.F. chlorides varied between 554 and 738 mgm per 100 c.c., the average figure being 649 mgm per 100 c.c.

**Organisms.**

In five cases the first lumbar puncture was reported to have Gram negative diplococci resembling...
meningococci in the direct films from the deposit, and pneumococci were isolated only from later specimens. In all five cases the initial lumbar puncture was carried out before admission and the accuracy of the observation cannot be estimated, although, as is noted on page 9, two of the cases behaved clinically like meningococcal meningitis at first.

The typical finding on direct film is a large number of Gram positive diplococci morphologically identical with pneumococci, some intracellular but many extracellular. In at least three cases the pneumococci were reported being in large numbers on direct film, while the cells were relatively scanty. In these cases the cerebrospinal fluid is described as evenly hazy and forming no sediment in two cases and only a powdery sediment in the third.

The pneumococci concerned was typed in twenty-three cases. The number of groups involved was fourteen, and the distribution is tabulated below.

<table>
<thead>
<tr>
<th>Group</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>11</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>21</th>
<th>23</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
Amount Removed

The amount removed is not in every case recorded where lumbar puncture was performed prior to admission. In the thirty-one cases in which the information is available the average amount removed at the first lumbar puncture was 26.6 c.c., the greatest amount being 60 c.c. removed from a woman of fifty-one years, on the day of onset of the disease.

Subsequent Lumbar and Other Punctures

The results of later lumbar and cisternal punctures are considered later with the response to treatment, and are summarised in Appendix 6.

TREATMENT AND PROGRESS

At this point it becomes convenient to subdivide the cases of pneumococcal meningitis according to the periods previously described on page 2.

PRE-SULPHONAMIDE PERIOD (1930 to 1937 inclusive)

Ten cases fall within this period. The record is a short and gloomy one.

Eight of the cases were admitted to hospital between the second and sixth days of disease, the average being third day. The history in the remaining two is not clear on this point.
Six of the patients survived less than twenty-four hours, and five of these received no form of treatment other than sedatives. The sixth of these cases and the remaining four of the pre-sulphonamide group received only the initial doses of anti-meningococcal serum, having been admitted as cases of meningococcal meningitis. None of the cases lived longer than two days in hospital, death occurring on the third to twelfth day of illness, or on the fifth day on an average.

The mode of demise appears to have been by progressive worsening of the meningeal symptoms, ending in deepening coma and final circulatory and respiratory failure, the temperature and pulse remaining high and tending to rise terminally.

During this period six lumbar punctures and one cisternal puncture were performed on the day following the initial puncture, and one lumbar puncture on each of the next two consecutive days. The general characteristics showed no change, and the average amount removed was 27.5 c.c.

Temperature charts are reproduced in Appendix 7.
Six of the patients survived less than twenty-four hours, and five of these received no form of treatment other than sedatives. The sixth of these cases and the remaining four of the pre-sulphonamide group received only the initial doses of anti-meningo-coccal serum, having been admitted as cases of meningococcal meningitis. None of the cases lived longer than two days in hospital, death occurring on the third to twelfth day of illness, or on the fifth day on an average.

The mode of demise appears to have been by progressive worsening of the meningeal symptoms, ending in deepening coma and final circulatory and respiratory failure, the temperature and pulse remaining high and tending to rise terminally.

During this period six lumbar punctures and one cisternal puncture were performed on the day following the initial puncture, and one lumbar puncture on each of the next two consecutive days. The general characteristics showed no change, and the average amount removed was 27.5 c.c.

Temperature charts are reproduced in Appendix 7.
SULPHONAMIDE PERIOD (January 1938 to September 1944)

During this period forty cases of pneumococcal meningitis occurred, of which six recovered. The average fatal case was admitted on the fifth day of disease and survived six days in hospital, dying on the tenth or eleventh day of disease. Twelve patients died on the day of admission to hospital or on the following day. If these patients, who had little opportunity to respond to treatment, are excluded, the average stay in hospital was nearer nine days, and death supervened on the thirteenth day.

The average non-fatal case was admitted on the second day of disease and was discharged after a stay of thirty-one days in hospital.

Sulphonamide Treatment - Fatal Cases

Case 11, the first case, was treated with Soluseptasine (a 5% solution of disodium - para (phenyl - propylamino) benzene sulphonamide for parenteral administration), and received 12c.c. intrathecally (0.6Gm. sulphonamide) and 45c.c. intramuscularly (2.25 Gm.) including 5c.c. given before admission. The intrathecal injection was given under general anaesthesia on the afternoon of admission. The child was very restless after recovering from anaesthesia, answering questions "in a strangled voice" and complaining of slight headache. He fell asleep at 10 p.m. At 11.15 p.m. breathing became laboured, and in spite of clearing the throat of mucus the boy became cyanosed and died thirty minutes later. This case is complicated by a history of injury prior to the onset of meningitis so that one is unable to say whether it was the effects of the injury or the meningitis or the sulphadiazine which caused the restlessness after lumbar puncture.
Cases 12, 13 and 14 received Sulphapyridine in the form of M & B 693 and M & B 693 soluble.

Case 12, an adult, received 20gms intravenously and 20gms by intramuscular injection, followed by two further intravenous injections of 20gms and then 16gms two hourly by mouth. No improvement ensued and she died after five days.

Case 13, an infant six months old, received 10gms intramuscularly on two occasions and also 0.50gms four hourly by mouth. The child, however, although admitted on the second day of disease died within twelve hours.

Case 14, was given 20gms Sulphapyridine intravenously and 20gms intramuscularly, followed by 16gms two hourly. Owing to difficulty in taking by mouth, he was given a further 40gms intramuscularly twenty-four hours later and oral administration was replaced by running in 20gms of Sulphapyridine four hourly by nasal catheter. Deterioration was not averted and the patient died on the sixth day of disease after five days in hospital.

Case 15 received no Sulphonamide treatment.

From this point onwards, that is from mid-1944, a basic pattern of dosage was adopted. This basic pattern may be represented as follows, the actual dosage being varied according to age.

<table>
<thead>
<tr>
<th>Initial dose 2x Gms intravenously, intramuscularly or by mouth.</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>x Gms two hourly for forty-eight hours.</td>
<td>24x</td>
</tr>
<tr>
<td>x Gms four hourly for forty-eight hours.</td>
<td>12x</td>
</tr>
<tr>
<td>x Gms three times daily for three days.</td>
<td>9x</td>
</tr>
<tr>
<td><strong>Total Basic Course</strong></td>
<td><strong>47x</strong></td>
</tr>
</tbody>
</table>

In infants under one year \( x = 0.25 \)
In children between one and twelve years \( x = 0.5 \)
In patients over twelve years \( x = 1.0 \)
Thus infants received 11.75 Gms in the full course, children between the stated ages 23.5 Gms, and older children and adults 47Gms.

This standard course was in many cases not adhered to strictly, variations being made to allow for previous dosage with sulphonamides, difficulty in making the patient take or retain the drug, and for various reasons connected with the patient's general condition. Many of the fatal cases did not, of course, complete the first course, but a number of cases required second courses in full or in part. In some of the later cases a dosage of $\frac{X}{3}$ three times daily for three days was added to the standard course. The dosage employed in each case is summarised in Appendix 6.

The drug used most was Sulphapyridine, which was used alone in twenty-five cases.

Case 27 had one course of Sulphapyridine followed by a pause for six days, after which Sulphapyridine therapy was restarted. After the second day of this course the drug was changed to Sulphanilamide in the form of Prontosil Album. This and Case 11 are the only cases in which Sulphanilamide was used.

Beginning in 1943 Sulphathiazole and Sulphadiazine were taken into use. The former was used in three cases and the latter in two.
Thus infants received 11.75 Gms in the full course, children between the stated ages 23.5 Gms, and older children and adults 47 Gms.

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Beginning in 1943 Sulphathiazole and Sulphadiazine were taken into use. The former was used in three cases and the latter in two.
As treatment was in most cases not completed before death, it is of no great value to analyse the total amount of sulphonamide administered.

The temperature charts of cases are reproduced in skeleton in Appendix 7, with the dosage indicated diagrammatically.

Recoveries

The six patients who recovered during the "Sulphonamide Period" were treated with Sulphapyridine. The ages of the patients were respectively 13, 36, 17, 16, 34 and 7 years. All except the last case thus fall within the age group receiving full dosage of Sulphonamides.

None of the cases required more than one course, but in each case the standard course described above has been exceeded in one way or another.

In case 19 the two hourly dosage was continued for four days instead of two, and the three times daily dose was stopped after one day, being discontinued on the appearance of a Sulphonamide reaction. The total dosage was 53Gms in seven days.

The patient was still pyrexial at the end of the course of treatment, but the temperature returned to normal a few days later.

Eleven days after admission C.S.F. protein, glucose and chlorides were all lower than at the initial lumbar puncture, but eight days later protein had dropped towards normal, while the glucose and chlorides had risen towards normal values. No organisms were seen in either specimen, and the fluid was only slightly hazy.
Case 22 had 10Gm Sulphapyridine by mouth before admission, was given 30Gm intravenously on admission, after which the dosage by mouth was supplemented and at times replaced by parenteral administration, the total amount of sulphapyridine given by all routes being 80Gms in eleven days. After a few days delirium requiring morphine and paraldehyde, the patient's condition improved steadily.

Case 26 was given 70Gms Sulphapyridine in twelve hours prior to admission. The initial parenteral dose was therefore omitted from the standard course, but the course was extended by the additional administration of 0.5 Gm three times daily for three days, bringing the aggregate to 53.5 Gms in ten days. The pyrexia subsided rapidly and did not recur although a sulphonamide eruption appeared on the ninth day of treatment.

In Case 34 the dosage in the three times daily period was 2Gms instead of 1Gm, and once more an extra three days of 0.5 Gm three times daily was added, bringing the total to 60.5Gms in ten days. The temperature dropped to normal in three days, and apart from a sulphonamide rash which appeared on the sixth day of treatment progress was good. The patient was allowed up on the twentieth day of disease and discharged fit one week later.

The fifth adult (Case 36) received the standard course with the addition of 2Gms intravenously on the second day and an extra three days of 0.5Gm three times daily. This brought the total once more to 53.5 Gms in ten days. Progress was uneventful after the first week apart from a headache on the 17th day.

Case 38, a boy of seven years, was given half the dosage given to Case 36, with the exception that two hourly dosage was continued for two and a half days instead of two days. The total Sulphapyridine given was 26.25 Gms in 11 days. Eight days after admission the child was rational and lively, and progress thereafter was steady.

Lumbar puncture on the twenty-second day produced clear, sterile fluid with the chemistry within the limits of normal.
The adults therefore received an average of 60 Gms given in one course of decreasing doses lasting approximately ten days, while the child had a comparable course when age is taken into consideration, it being accepted that the dosage for children must exceed the figure indicated by Young's or similar formulae.

SECOND and SUBSEQUENT LUMBAR PUNCTURES

During the Sulphonamide Period eighteen punctures were performed after treatment was started. The days on which these later punctures were carried out are shown diagrammatically in Appendix 9.

It will be seen that nine were performed in the first week of treatment, five in the second week and three later than this.

The changes in Cases 19 and 38 have already been alluded to. No final punctures were performed in the other recovered cases.

In the fatal cases, although in some patients the turbidity decreased and protein became less, in all cases the pneumococci continued to be found in direct films. The sugar and chloride content tended to remain low.
PENICILLIN PERIOD (October 1944 to March 1946)

This period is for convenience described as the Penicillin Period, but it must be understood that the majority also received Sulphonamides in some form as well as Penicillin.

Eight cases only fall within this period. Of these, four died and four recovered.

Fatal Cases

The four patients who died were aged forty-one years, eight months, seven years and sixty-seven years. They were, on average, admitted on the third day of disease, and survived respectively until the fifty-first, twenty-seventh, eight and tenth days, an average survival period of twenty-four days.

In Case 51, a woman aged forty-one years, suffering also from empyema, treatment was started with Sulphathiazole 2 Gms intravenously and Sulphapyridine 2 Gms intramuscularly, followed by Sulphamezathine (Sulphadimethylpyrimidine) 1 Gm two hourly for three days. After two days of this course Penicillin treatment was started with 60,000 units intramuscularly four hourly, and for the following four days 10,000 units of Penicillin was administered intrathecally daily by lumbar puncture. Meanwhile, the course of Sulphamezathine was completed by giving 1 Gm four hourly for two days, 1 Gm three times daily for three days and 0·5 Gm three times daily for a further three days. Lumbar puncture three days later produced clear, sterile fluid under normal pressure, the protein remaining high at 150 milligrammes per hundred millilitres, and the meningitis appeared to have been cured. The pleural cavity still contained pneumococcal pus, however, and
treatment for the next three weeks was mainly directed to this region. Lumbar puncture on the twenty-seventh day, following a complaint of headache, produced a normal fluid except for a very considerable increase in the protein content (600 mgm. per 100 ml.) on the 40th day acute meningeal signs reappeared. Treatment was recommenced on the following day in the form of 60,000 units of Penicillin four hourly intramuscularly. This dose was reduced on the following day to 20,000 units four hourly for fifteen doses, and thereafter raised once more to 60,000 units four hourly for three doses. On this last day Sulphamezathine treatment was resumed at the rate of 1.5 Gm four hourly, and a further series of four daily intrathecal injections of 10,000 units of Penicillin. Following this, intramuscular doses of 60,000 units four hourly were resumed until the patient died two days later.

Excluding 13,000 units injected into the empyema cavity, the total Penicillin administered in this case was 2,180,000 units. The sulphonamides given amounted to 61.5 Gms in the first course of eleven days, and a further 54 Gms in the second course of six days, making 115.5 Gms in all.

This case exhibits many interesting features, including various cranial nerve palsies, and is reproduced in some detail in Appendix 7.

The bacteriostatic power of the C.S.F. is of particular interest as considerable bacteriostasis was attained prior to institution of intrathecal Penicillin therapy.

Case 53, an infant of eight months, received 3.5 Gms Sulphathiazole and 2 Gms soluble Sulphapyridine in three days before admission. On admission on the fourth day Sulphathiazole treatment was continued with 1 Gm intramuscularly followed by 0.25 Gm two hourly for two days, four hourly for two days and three times daily thereafter, bringing the total to 28.75 Gms in twenty-seven days. Starting on the day after admission six doses of 60,000 units of Penicillin were given intramuscularly at four hourly intervals. Four daily intrathecal doses of 10,000 units of Penicillin were given. The child's condition improved considerably but meningeal signs reappeared after two days, and a second series of ten daily intrathecal injections of 10,000 units was administered. The total Penicillin given was 500,000 units.
Case 54, a boy aged seven years, admitted on the third day of disease, was given 1 Gm Sulphathiazole intravenously followed by 0.5 Gm Sulphathiazole two hourly for one day, four hourly for three days and three times daily until death, or 18 Gms in a little under six days.

A course of four daily intrathecal injections of 10,000 units was the only Penicillin given in this case.

The cerebrospinal fluid reports showed considerable improvement. The last lumbar puncture produced clear fluid of normal pressure, sterile, and containing few cells, mainly lymphocytes, but it was on this day that the child died. A moderate growth of pneumococci was obtained from pus found round the base of the brain.

Case 56, the remaining fatal case, a man of sixty-seven years, admitted on the third day of disease, was treated with continuous intramuscular Penicillin administered at the rate of 200,000 units daily by "Fudrump", together with five daily intrathecal doses of 20,000 units of Penicillin. Concurrently Sulphadiazine 2 Gms intravenously followed by 0.75 Gm two hourly for two days, 1 Gm four hourly for two days, and 1 Gm daily for the remaining four days of life.

The response to treatment was fairly good, but the temperature rose again after cessation of Penicillin therapy, and the patient died suddenly when held up to pass urine.

Recoveries

The patients who recovered were aged sixty-five years, twenty-three years, seven weeks and fifty-four years, and were admitted on the first, third, fifth and sixth days of disease respectively. On average they were discharged after seven weeks.
Two cases received Penicillin alone, one was treated with Penicillin and Sulphathiazole, and the other with Penicillin and Sulphadiazine.

Case 52, a man of sixty-five years, was admitted on the day of onset and was given 50,000 units of Penicillin four hourly for six doses intramuscularly, and starting in the second day of disease four daily intrathecal injections each of 10,000 units of Penicillin, so that the complete course comprised 400,000 units given in less than five days. Once more the bacteriostasis estimation showed effective stasis by neck C.S.F. before any intrathecal Penicillin had been given. Improvement was rapid and this also had commenced before the first intrathecal Penicillin injection.

Case 55, already quoted earlier, was a Polish service patient, aged twenty-three years, suffering from gunshot wounds of head.

On admission he was given 2 Gms Sulphathiazole intravenously followed by 0.75 Gm two hourly for two days, 1 Gm four hourly for four days, and three times a day for a further four days, or 56 Gms in all. Penicillin was administered intrathecally in five daily doses of 20,000 units commencing on the day after admission. This was supplemented by six doses of Penicillin at four hourly intervals by the intramuscular route, followed after a gap of one day by the setting up of a continuous intramuscular injection of penicillin by "Endrip" at the rate of 200,000 units daily until 2,340,000 units had been given, making a total of 2,700,000 intramuscularly and 100,000 intrathecally. There was no improvement for three days, but after five days improvement was marked, although the patient was left with a bilateral nerve deafness when he was transferred back to the care of the Polish medical authorities.

Case 57, the youngest in the series, an infant aged seven weeks, admitted on the fifth day of disease, was treated with intrathecal Penicillin, 20,000 units daily for five days, concurrently with 20,000 units intramuscularly four hourly for approximately five
days. The pyrexia took over ten days to subside, but the child made an apparently full recovery, and was discharged after six weeks in hospital. No sulphonamide was given.

Case 58, a woman of fifty-four years, was given 2 Gms Sulphadiazine intravenously followed by 0.75 Gm two hourly for two days, then 1 Gm four hourly for two days and three times daily for three days; that is, 41 Gms in seven days.

Penicillin was given intrathecally 20,000 units daily and intramuscularly 100,000 units daily by continuous "Endrip" for five days, bringing the total to 100,000 units intrathecally and 500,000 units intramuscularly, or 600,000 units in all.

SUPPLEMENTARY FORMS OF TREATMENT - ALL PERIODS

In all cases during all three periods various other factors and forms of treatment contributed towards the patients' progress. The principal ones are enumerated below.

Primary Focus

Where a primary focus was evident treatment was, of course, directed to eradicating this.

Lumbar Puncture

As distinct from diagnostic punctures and those done to introduce sera or antibiotics, repeated lumbar puncture was not employed as a form of treatment, but when it was performed the opportunity was taken to draw off as much fluid as possible to help relieve
intracranial pressure. General anaesthetics were frequently used to quieten the patient during lumbar puncture.

Retention

The occurrence of retention has already been alluded to, and carbachol or catheterisation gave relief where necessary.

Sedatives

The irritability and headache were in many cases sufficiently severe to require full doses of morphine or other opium derivatives, with or without hyoscine, for their relief. This is more noticeable in the older patients than the younger, but no age is immune. Less powerful drugs, such as chloral or paraldehyde, were also employed, while in the less severe stages aspirin gave sufficient ease in some cases.
MENINGITIS DUE TO *HAEMOPHILUS INFLUENZAE*

For convenience the term "Influenzal Meningitis" will be used to indicate meningitis due to haemophilus influenzae, although it is recognised that haemophilus influenzae is not the primary causal organism in influenza.

Twenty-five cases of influenzal meningitis appear in the City Hospital records in the thirty years ending March 1946.

**ANNUAL INCIDENCE**

The recorded cases are few and far between before 1930. There are in fact only two cases, one in 1919 and one in 1922. After 1930 there was one case in 1931, 1932, 1933, 1935 and 1940, and two in 1936. In the next five and a quarter years there occurred an average of three cases a year spread more or less evenly over the years. (Appendix 1)

**SEASONAL INCIDENCE**

The cases were fairly evenly distributed throughout the year, although five cases commenced in May and four in October.

**AGE DISTRIBUTION**

The patients were mostly infants, the youngest being two months old. Twelve (48%) of the patients
were under one year old. A further six (24%) were less than two years old, two (8%) were two years old, two (8%) three years old, and one five years of age. The remaining two were aged thirteen and forty years of age.

SEX DISTRIBUTION

Males outnumbered females by sixteen to nine (64% to 36%) over the series.

CLINICAL FEATURES

Two of the cases fell in the pre-record period and the case notes of three of the later cases were unfortunately not found. Henceforth this report will deal only with the remaining twenty cases.

PRIMARY FOCUS

Case 59 was a female child, two years of age, from a country district. A history was given of severe "influenza" in three local farms including the farm at which she lived.

Case 60 had a chronic otitis media which dried up nine days before admission.

At the postmortem examination of case 62, an infant of eight months, H. influenzae was isolated from a swab taken from the lung.

Case 70, aged five years, had a history of acute otitis media six weeks previously but no signs of active otitis media on admission.

Case 72, aged two and a half years, had a running nose a week before onset.
In case 73 bronchopneumonia preceded the meningitis.

Case 78 had a history of a "feverish cold" a few days before the onset of meningitis.

The history in the remaining cases gives no indication of a possible primary focus.

It is not claimed that the events noted above were in every case responsible for the onset of the meningitis, but some of the histories are at least suggestive.

The proportion of cases of "influenzal" meningitis in which a preliminary diagnosis of meningococcal meningitis was made on the first lumbar puncture was high, Gram negative diplococci having been described in six cases on examination of direct films.

HISTORY and SYMPTOMATOLOGY

Headache appears in the history of all the cases over the age of twenty months with the exception of case 59, aged two years and ten months, who was unconscious on admission. The presence of this symptom in younger children can, as in the case of pneumococcal meningitis, only be inferred from the presence of other signs.
Shivering or Malaise is specifically mentioned in six of the cases.

Vomiting is a prominent symptom and occurred in sixteen of the twenty cases.

Bowel movement. No mention is made of the presence or absence of constipation except in case 77, an infant who suffered from diarrhoea.

Disturbances of Consciousness. Three children (cases 62, 72, and 75) became drowsy or semiconscious, and four became comatose. Restlessness or irritability was evident in seven cases, and delirium in four, in one of which (case 72) the child, aged two and a half years, had intermittent spasms of maniacal excitement.

Convulsions or localised twitchings are mentioned in one quarter (5) of the cases.

**CLINICAL FEATURES on ADMISSION**

**Day of Disease on admission**

Excluding case 78, in which the history appears to date back over one month, the average case was admitted on the fifth day of disease. One case was admitted on the day of onset, four on the second day, five on the fourth, one each on the fifth and sixth, four on the seventh day, and one each on the eighth and tenth day.
Temperature on Admission

The temperature on admission varied between subnormal and 104°F. The average was 100.8°F.

Pulse on Admission

The pulse varied between 72 per minute in the adult and 190 per minute in an infant. The average pulse rate was about 130 per minute and shows a rise more or less consistent with the rise in temperature.

Respiratory Rate on Admission

On the whole this was somewhat raised, the average being 30 per minute, if the two cases suffering also from pneumonia are excluded.

General Condition on Admission

Most of the patients were in poor general condition with some signs of complete or partial loss of consciousness, together with irritability in some degree.

SIGNS OF INCREASED INTRACRANIAL PRESSURE OR IRRITATION

Neck Rigidity

Apart from cases 76 and 77, both of which had convulsions, neck rigidity was present in every case (90%) and marked in five of these (25%).

Head Retraction was present in four cases (20%).

Opiathconus is not recorded in any case.

The Anterior Fontanelle was recorded bulging in
three patients (15 %) and depressed in one patient.

Kernig's sign was positive in fifteen cases, being marked in three of these cases, and slight in a further three.

**SIGNS OF INTERFERENCE WITH NERVE PATHWAYS**

**Tendon Reflexes**
The knee jerk was bilaterally absent in three cases (15 %), bilaterally present in six cases (30 %), and unilaterally absent on one side in one case, and unrecorded in the remainder, possibly due to difficulty in eliciting the sign in irritable infants.

**Superficial Reflexes**
The abdominal reflexes were absent in nine cases, diminished in one case, present in six, and unrecorded in four.
The plantar reflexes were flexor in eight patients, extensor in two, and unrecorded in the remaining ten cases.

**Urinary Retention** was not recorded in any case.

**Eye signs**
Strabismus appears in the notes of only two (10 %) of the cases.

There was no other definite abnormality except a lateral nystagmus in the adult patient, and sluggish reaction to light accompanied by dilated pupils in two infants (cases 64 and 65).
Other Signs

Case 60 had indefinite signs of mastoiditis, and mastoidectomy was performed two days later.
Case 64 had a large hydrocephalic head and thin body.

CEREBRO-SPINAL FLUID FINDINGS

In all eighty-two lumbar punctures, six cisternal punctures and one ventricular puncture were carried out on the twenty patients involved.

Of these twenty lumbar punctures were performed before admission to City Hospital, and only five cases were admitted without prior lumbar punctures having been carried out.

Time of First Lumbar Puncture

On average the first lumbar puncture was performed late on the fourth day of disease. The four who recovered had the first puncture on the first, second or third day. If these are excluded the average fatal case was not lumbar punctured until the fifth day of disease.

Pressure

As in pneumococcal meningitis the pressure was usually increased, and is described as under normal pressure in only one case. No manometric readings were taken.
Appearance

In one case the fluid is described as hazy, but in all other cases as turbid. On settling, the deposit is usually described as greyish or whitish. No other colour is mentioned.

Cells

The fluid contained large numbers of cells with an overwhelming predominance of polymorphs. Only in one case were the predominant cells lymphocytes.

Chemistry

The C.S.F. chemistry is recorded in only six of the cases, mainly because such a high proportion of first lumbar punctures were done before admission. Protein. The average figure for protein was 156 mgm per 100 c.c., the extremes being 75 and 300 mgm per 100 c.c.

Sugar. Glucose varied from nil to 37 mgm per 100 c.c., the average figure being 10 mgm per 100 c.c.

Chlorides. C.S.F. chlorides ranged from 632 to 773 mgm per 100 c.c., averaging 680 per 100 c.c.

Organisms

In eight cases out of the twenty haemophilus influenzae was not recognised in the first lumbar puncture and the case was provisionally diagnosed meningococcal meningitis, scanty small Gram negative
cocobacillary forms having been misinterpreted as meningococci.

Typically the direct film showed small Gram negative cocobacilli, short rods and filamentous but imbrancking forms, yielding *H. influenzae* on culture.

The organisms were not typed.

Amount Removed
The amount drawn off varies from 40 c.c. in a child under three years to 10 c.c., with a mean figure of 23·3 c.c.

Subsequent Lumbar and Other Punctures
These are reported along with the results of treatment, and summarised in Appendix 6.

TREATMENT and PROGRESS
Sulphonamide treatment of Influenzal Meningitis was not started until 1941, so that the pre-sulphonamide period must in this case be lengthened to the end of 1940.

PRE-SULPHONAMIDE PERIOD (1930 to 1940 inclusive)
Five cases fall within this period (cases 59 to 63). They were admitted to the City Hospital on the ninth, tenth, seventh, seventh, and fourth days respectively. The average case was therefore admitted on the seventh day.
One case received no treatment and died within twenty-four hours of admission to hospital.

The remaining four cases, having been admitted with the provisional diagnosis of meningococcal meningitis, were given intrathecal antimeningococcal serum until the diagnosis of influenzal meningitis was confirmed. Naturally enough the serum produced no curative result, but the opportunity was taken to reduce the intracranial pressure.

In case 59, for instance, the patient, a child of two years and ten months, had a total of fourteen lumbar punctures during which an aggregate of over 410 c.c. of C.S.F. was removed, to be partially replaced by 128 c.c. of serum.

In case 60, a woman of 40, at the fifth lumbar puncture needles were inserted in the second and fourth spaces and saline washed through from one to the other, washing out pus and fibrin flakes. This woman also had a mastoidectomy performed on the previous day. No pus or active inflammation was found, but there was evidence of previous inflammation and sclerosis.

The C.S.F. showed no obvious changes on successive punctures except increase in turbidity. Chemical analyses were not carried out.

The temperature and pulse records show irregular pyrexia of no defined pattern. One case had a terminal hyperpyrexia.

The average case died on the twelfth day of disease.
SULPHONAMIDE PERIOD (1941 to 1944 inclusive)

During this four year period eleven cases were treated with sulphonamides only. Three of these recovered.

Sulphonamide Treatment - Fatal Cases

The average fatal case was admitted on the fifth day of disease, survived twenty-seven days, and died on the thirty-first day, the variation being between thirteen and sixty-one days.

The first six cases were treated with Sulphapyridine.

One case was treated with Sulphathiazole and the remainder primarily with Sulphadiazine.

The general lines of treatment were the same as those observed in treating pneumococcal meningitis. Each course of sulphonamides consisted of progressively diminishing doses and lasted about ten days.

Case 64, aged twenty-two months, received 25 Gms in six days but failed to respond. The temperature rose in the two days before death. Postmortem examination showed the presence of acute suppurative meningitis, subdural abscess which appeared to be chronic, and hydrocephalus.

Case 65, aged eight months, was given a course of 9.5 Gms in 10 days during which time the child was apyrexial. Three days later the temperature suddenly rocketed to 103.2°F and later to 104.2°F and the child died on the following day. A point of interest in this case is that in spite of dehydration and depressed fontanelle, the child was prior to death in a state of extreme opisthotonos.
Case 66, aged nineteen months, differed from the previous two in exhibiting a swinging temperature throughout with a diurnal variation frequently greater than three degrees Fahrenheit. During the last four days the temperature dropped to normal but a further kick up to 100°F preceded death.

Case 67, aged eighteen months, had an even more irregular temperature chart. After an apparent improvement in the first six days a relapse occurred in spite of continuance of treatment with a full course of sulphapyridine. A further similar course was given, again with reduction in temperature but worsening of general condition which continued until death on the forty-fifth day of disease.

Case 68, aged three and a half years, improved after a course of just over 25 Gms Sulphapyridine. After a further fortnight the patient's condition deteriorated steadily and in spite of a further similar course the patient died on the forty-sixth day. The child was a pyrexial during the last week of life.

Case 69, nine weeks old, was in poor condition on admission and did not respond to a course of 13.5 Gms Sulphapyridine. The temperature was normal or sub-normal throughout.

Case 71, aged twenty months, showed no demonstrable response to a course of 16 Gms of Sulphathiazole, and died on the sixteenth day. The temperature was raised throughout and reached 105°F shortly before death.

Case 74, aged ten months, was admitted on the fourth day and responded to a course of approximately 12 Gms Sulphadiazine in ten days. Lumbar puncture after the course produced clear fluid under normal pressure. On the following day the temperature began to rise, and three days later lumbar puncture produced purulent fluid once more. A further similar course of Sulphadiazine produced transient improvement but a third similar course was necessary. Again there was definite improvement but vomiting was troublesome and two days after the end of the third course Sulphadiazine soluble 0.5 Gms was administered by intravenous drip along with 5% glucose. However, the infant's general condition deteriorated, and the child died on the sixty-first day, the temperature having risen steadily during the final four days.
Sulphonamide Treatment — Recoveries

Three cases (27.3%) recovered during this period.

They were admitted on the first, second and fourth day of disease, and were discharged on the 35th, 37th and 54th day respectively.

Case 70, aged five years and nine months, was admitted on the day of onset of meningitis and pneumonia. He had been given 1.5 Gms Sulphathiazole before admission and was given a course of 22.75 Gms Sulphadiazine in the first ten days. All appeared to be going well; however, lumbar puncture on the 21st day produced clear fluid under normal pressure but containing haemophilus influenzae on culture. Three days later the temperature rose. A course of 11.5 Gms of Sulphathiazole was given, with rapid response, and the child was discharged fit on the thirty-fifth day.

Case 72, age two and a half years, was admitted on the second day of disease, was given 1.5 Gms Sulphathiazole before admission and this was followed on admission by a course of 27 Gms Sulphadiazine in ten days. The response to treatment was satisfactory and check lumbar puncture on the 27th day produced clear fluid under normal pressure and containing only a few lymphocytes and slightly raised protein. The child was discharged well on the 37th day.

Case 73, aged ten months, had been given 3 Gms Sulphapyridine for bronchopneumonia before admission and made an apparent recovery. Three days before admission the child had convulsions and was admitted to another hospital where it received 3 Gms Sulphamethazine before admission to the City Hospital where it was given a course of 12 Gms Sulphadiazine in eight days. On the last day of this course the child's condition relapsed. A second course of 10.5 Gms Sulphadiazine in nine days resulted in improvement for a few days but on the twenty-fourth day the temperature rose again and lumbar puncture two days later produced slightly turbid fluid containing organisms resembling H.influenzae. A third course of 14 Gms in ten days once more led to improvement and the child was discharged on the fifty-fourth day.
PENICILLIN PERIOD (1945 to March 1946)

During the fifteen months of this period four cases only were admitted. Of these one died within twelve hours of admission and received no specific treatment.

Of the remaining three cases, two died. They were infants of ten months and four months admitted respectively on the fourth and second days of disease.

Case 75, aged ten months, was treated with a course of 20,000 units of Penicillin in 4 c.c. intrathecally on five consecutive days. Four days later lumbar puncture produced a small quantity of bloodstained fluid which was apparently sterile. The pyrexia continued and a course of Sulphathiazole was started. The child was apparently unable to retain the tablets and daily intramuscular injections of 1 Gm were given, bringing the total course to approximately 24 Gms in nine days. The temperature gradually subsided, but two days later the child died.

Case 77, aged four months, who was admitted on the day following onset, was treated with six doses of 20,000 units Penicillin in 4 c.c. intrathecally daily except the second day when two doses were given. Intramuscular Penicillin 20,000 units four hourly were given after the intrathecal dosage but without avail and the child died on the thirteenth day.

Case 78, aged three years, recovered. There was a history of a feverish cold about five weeks before admission during which, at one stage, the child became drowsy and restless. Two courses of Sulphathiazole failed to produce lasting improvement and the child was admitted to another hospital where 30,000 units Penicillin was injected intrathecally on three days, and a total of 450,000 units injected intramuscularly over the same period. On admission to City Hospital, a course of six daily intrathecal injections of Penicillin 20,000 units in 4 c.c. were given, together with a course of 25 Gms Sulphathiazole in nine days. The temperature fell to normal in less than five days.
The child was allowed up on the 16th day after admission and discharged home twelve days later.
STREPTOCOCCAL MENINGITIS

This is a considerably smaller group than the preceding two, and includes fourteen cases only in the thirty year period in question.

Two cases are recorded prior to 1930. Five fall in the pre-sulphonamide period after 1930, five in the sulphonamide period and the remaining two in the penicillin period.

One of the last two cases was the only survivor of the fourteen.

ANNUAL INCIDENCE

The cases were sporadic, and not more than two occurred in any one year. The distribution is shown in Appendix 1.

SEASONAL INCIDENCE

Three cases occurred in each of the three months October, November and January. Twelve occurred in the winter six months of the year and two in the summer six months. (See Appendix 3)

AGE DISTRIBUTION

The ages vary from three months to sixty-seven
years. Three (25%) were under one year old, seven under ten years old, and ten under twenty years of age. The remaining four were aged 20, 36, 39 and 67 years. (See Appendix 4)

SEX DISTRIBUTION

As distinct from pneumococcal and influenza meningitis, the sexes share equally in the fourteen cases, except in the under twelve months group where there are three males and no females.

CLINICAL FEATURES

Records are available for all except the first two cases.

PRIMARY FOCUS

A high proportion had some other lesion which was probably the primary focus.

Case 83 had enlarged and septic tonsils and septic mouth.

Case 84 had pleurisy of some months standing. No tubercle bacilli were found. There may well be no connection between the pleurisy and meningitis.

Case 86 had been suffering from gastroenteritis of unknown origin. (See page 121)

Case 87 was suffering from streptococcal septicaemia, proved by blood culture.

Case 89 complained of earache five days before
admission. No otorrhoea is recorded.

Case 90 gave a history of pyelitis several weeks before admission. The time of onset of the meningitis is difficult to determine. Acute symptoms appeared six days before admission but hydrocephalus was already present on admission.

Case 91 had a discharging left ear and pneumonia. There is, unfortunately, no record of the organism concerned in the otorrhoea.

Case 92 was suffering from acute bacterial endocarditis, with embolic nephritis, hypostatic pneumonia and other phenomena secondary to the endocarditis. S. viridans was found in the vegetation.

Case 94 had suffered from intermittent otorrhoea since measles three years previously.

In the remaining three cases there is nothing significant in the history.

MODE OF ONSET

Headache is once more the predominant symptom, being reported in all cases over one year of age. The headache was particularly severe in four cases, aged 17, 36, 50 and 67 years.

Malaise or Shivering is recorded in four cases and rigors in two of the adult cases.

Vomiting appears in the history of eight (67%) of the patients.

Constipation is specifically mentioned in regard to three cases.
Retention was not noted in any of the cases.

Disturbances of Consciousness.

Three patients were "drowsy", four "semi-conscious", three irritable and two delirious, while an infant of three months and a man of fifty years had a record of convulsions.

The oldest patient had localised twitching of the right arm and leg and loss of speech.

Symptoms referable to other lesions distinct from the meningitis, were of course, also present.

The case histories give the impression of a slower onset on the whole than in the case of the average pneumococcal meningitis.

CLINICAL FEATURES ON ADMISSION TO HOSPITAL

Day of Disease

The day of disease is, in several cases, difficult to estimate because of the presence of the other conditions previously detailed. An attempt has, however, been made to give a reasonable estimate in each case.
The average case was admitted on the seventh day. The patient who recovered was admitted on the fourth day, and the remainder on the first to the thirteenth day.

Temperature, Pulse and Respiations on Admission

The temperature on admission varied between 97.2°F and 104.2°F, the average figure being 99.9°F.

The pulse rate was increased in proportion to the age and temperature.

The respiratory rate showed corresponding increases with the exception of Case 91, suffering from pneumonia, and the three infants, where the rate averaged 44 per minute.

General Condition

This depended to a considerable extent on the concurrent primary condition and was variable. Disturbances of consciousness have already been considered with the history.

Signs of Increased Intracranial Pressure or Irritation

Neck Rigidity was recorded in ten cases, and marked in four of these.

Head Retraction was present in three of the cases.
Opiathotonos was not present in any case.

Bulging of the Fontanelle was marked in one of the three infants.

Kernig's Sign was positive in most cases, but negative in two cases, aged six months and fifty years.

Signs of Interference of Nerve Pathways

Tendon Reflexes

The knee jerks were recorded in seven cases, positive in all of these, and exaggerated in two of the seven.

Superficial Reflexes

Abdominal Reflexes are recorded in ten cases, of which five were negative, one doubtful, three positive and one exaggerated. No asymmetry was noted.

Plantar Reflexes. These were flexor and symmetrical in the five cases in which the sign was elicited.

Eye Signs

Ptosis was present in Case 91.

The Light Reflex was absent in two cases (89 & 93).

Otherwise no gross eye signs were present.
Other Nervous Signs

In addition to ptosis, Case 91 showed general hyperaesthesia, and localised twitching of the right arm, associated with impairment of speech.

CEREBROSPINAL FLUID FINDINGS

Thirty-six lumbar punctures, eleven cisternal punctures and one ventricular puncture were performed in the twelve patients. Eight lumbar punctures were performed before admission.

Initial Lumbar Puncture

The first lumbar puncture was performed on average on the seventh day of disease, the limits being second to thirteenth day.

Pressure

The pressure was not manometrically recorded but was regarded as low or normal in two of the seven cases in which the information is available. The increase in pressure was gross in one case.

Appearance

The C.S.F. was turbid in most cases, opalescent in two and clear in one. In this last case a further
lumbar puncture four days later, but still before admission, produced turbid fluid.

**Cells**

In three C.S.Fs withdrawn before admission a cell count was carried out, the counts being 10,000, 3,600, and 1,360 per c.mm. The pus cells were mainly polymorphonuclears, except in Case 88, in which lymphocytes and endothelial cells predominated.

**Chemistry**

The chemistry of the fluid drawn off at the first lumbar puncture was not recorded in sufficient cases to warrant analysis. Case 92 showed protein 1,500 mgm per 100 c.c., glucose 10 mgm per 100 c.c., and chlorides 606 mgm per 100 c.c.

**Organisms**

Gram positive cocci were reported in the first or "pre-treatment" C.S.F. in six cases (50%).

Gram negative diplococci were reported in four cases.

In the other two cases no organisms could be found.
Considering also the organisms found in later specimens, three cases were due to haemolytic streptococci and two to streptococcus viridans. The organism is unclassified in the remaining cases.

Amount Removed

The average amount removed in the seven cases where the information is recorded was 22 c.c.

Later Punctures

These are, as in the sections dealing with pneumococcal and influenza meningitis, considered along with response to treatment.

TREATMENT AND PROGRESS.

Pre-Sulphonamide Period (1930 to 1937 inclusive)

This period included five cases. The average case was admitted on the eighth day, survived four days and died on the twelfth day. The longest survival was seventeen days and the shortest nine days. There were no recoveries.

No specific treatment was given (other than anti-meningococcal serum until the true diagnosis became apparent).
Cases 83 and 84 died on the day after admission.

Case 85 had five lumbar punctures at which 257 c.c. fluid were withdrawn, to be partially replaced by 105 c.c. serum. Although the C.S.F. was turbid from the start streptococci were not found until the last two punctures. The temperature remained below 100°F throughout.

Case 86 had a continued pyrexia between 100°F and 105°F throughout. Gram negative diplococci were reported in the first specimen, but streptococci were found in all subsequent specimens which were obtained by cisternal puncture. The infant died after five days.

Case 87, a boy of eight and a half years, also suffering from streptococcal septicemia was admitted and treated as a meningococcal meningitis, the diagnosis being based on finding scanty Gram negative diplococci after prolonged search, before admission. Similar organisms were reported on the first two days after admission, but streptococci were found on the subsequent seven days and in blood culture on the day after admission. Cisternal puncture was necessary on two occasions. The temperature was hectic and reached 106°F on one occasion.

Sulphonamide Period (1938 to 1944 inclusive)

A further five cases were treated within this period. All were fatal.

The average case was admitted on the eighth day, survived twenty-six days, and died on the thirty-fourth day.

Two of the cases survived until the fifty-second and eighty-eighth day of disease respectively, and the other three died after three, two and one day in hospital.
Case 88, an infant of three months, was admitted on the ninth day of disease and received a course of 16 Gms Sulphapyridine in nine days, followed by a second course of 16.5 Gms Sulphapyridine in ten days. This was followed by a third course of 18 Gms Sulphanilamide in ten days, followed by a fourth four days later of Sulphanilamide 0.25 Gms two hourly for three days, followed by two daily doses of Sulphapyridine soluble. In spite of this prolonged dosage totalling 61.5 Gms of Sulphonamides in forty-three days, haemolytic streptococci continued to be isolated from each specimen of cerebrospinal fluid, and the child died on the fifty-first day.

During the course of the illness two lumbar punctures, two cisternal punctures and one ventricular puncture were carried out. The first lumbar puncture was performed before admission. A few Gram positive cocci were seen but were regarded as probable contaminants. The cisternal and ventricular punctures were carried out on the twenty-second, thirty-ninth and forty-eighth days respectively. The results are summarised in Appendix 6. It will be noted that the protein remained very high, the chlorides progressively diminished and the glucose dropped from 10 mgm per 100 c.c. to nil and rose again to 12 mgm per 100 c.c.

The character of the pyrexia is shown in Appendix 7 to be moderate but persistent.

Case 89, a woman of thirty-nine years, received the beginning of a standard course of Sulphapyridine such as described on page 23, but was in very bad condition on admission and died on the eighth day of disease, having received approximately 32 Gms of Sulphapyridine. Repeated morphia, chloral and bromide were required to quieten her.

Case 90, an infant six months of age, had had an unspecified but considerable amount of Sulphapyridine some few weeks prior to admission. The chart reproduced in Appendix 7 summarised the treatment and progress of the case. A total of 35 Gms Sulphonamides (Sulphapyridine, Sulphathiazole and Sulphanilamide) was given, divided into several courses. The child developed hydrocephalus and a total of 595 c.c. fluid was removed during nine lumbar and cisternal punctures. It will be noted that the protein on the whole increased and the glucose and chlorides remained low. Streptococcus viridans persisted until the second
last lumbar puncture. The last lumbar puncture produced sterile fluid but protein had increased and chlorides decreased. The child died on the eighty-eighth day.

Case 91, a woman aged sixty-seven years, survived only two days, and received only the first part of a course of Sulphapyridine. She had left otorrhoea and showed signs suggestive of a collection of pus, whether inside or on the surface of the brain in the region of the lower end of the Rolandic fissure, involving head, upper limb and speech area.

Case 92 died within thirty-six hours of admission and showed no outstanding features.

Penicillin Period (1945 to March 1946)

The remaining two cases, including the sole survivor, came within this period.

Case 93, a man of age fifty years, was in very bad physical shape, apart altogether from his meningitis, suffering as he was from acute bacterial endocarditis, generalised oedema, enlarged liver, hypostatic pneumonia and embolic nephritis. The meningitis (presumably blood spread by streptococcus viridans from the vegetations in the heart) proved to be the last straw and in spite of intrathecal and systemic penicillin reinforced by Sulphathiazole by mouth the patient died within twenty-four hours.

Case 94, a girl aged eight years and seven months, suffering from streptococcal meningitis which appears to have been secondary to right otitis media, responded rapidly to 20,000 units Penicillin in 4 c.c. intrathecally for five days (100,000 units), reinforced by 100,000 units Penicillin intramuscularly by "Endrip" daily for the same five days (500,000 i.m. in all), and by a course of Sulphathiazole 0.5 Gms two hourly for two days, four hourly for five days, and three times daily for two days, bringing the total to 30 Gms in nine days.
The otitis media and meningeal signs both subsided satisfactorily and the patient was allowed up on the twenty-fourth day and discharged fit on the thirty-first day.
MENINGITIS DUE TO OTHER ORGANISMS

The City Hospital records include only four cases of meningitis due to other cocci and bacilli, meningococcal and tuberculous meningitis being excluded. A staphylococcal case occurred before 1930.

Pneumobacillus Meningitis

Case 95, I.M., a female infant, aged ten months, was admitted on 26th August 1931 with a history of feverishness and vomiting nine days previously. Bulging of the fontanelle, neck rigidity and irritability were noted two days later. She was admitted as a case of meningitis and treated as such with daily injections of antimeningococcal serum for two days until Friedländer pneumobacillus was isolated from the cerebrospinal fluid. The case presents no points of distinction from the other forms of meningitis, and the patient died in hyperpyrexia on the fifteenth day.

Salmonella Dublin Meningitis

Case 96, A.D., a male infant aged five months, was admitted on the 11th May 1934 with a history of vomiting for two days three weeks previously, and anorexia since. Head retraction was first noticed eleven days before admission. On admission the outstanding points were well marked neck rigidity, head retraction and opisthotonos, with bulging fontanelle. The abdomen was scaphoid and the abdominal reflexes absent.

Cerebrospinal fluid was obtained by cisternal puncture, and was under pressure, turbid, glucose free and contained large numbers of polymorphs and a few Gram negative bacilli which later proved to be S. Dublin.
Before this result was obtained the case was treated for three days as a meningococcal meningitis and received three doses of 10 c.c. antiteningococcal serum. Thereafter the treatment consisted only of removing C.S.F. to relieve intracranial pressure. With the exception of the first occasion this was done by ventricular puncture.

The infant survived fourteen days, during which the one cisternal puncture and twelve ventricular punctures were performed. The total volume of fluid removed was 650 c.c. On each occasion the report was similar to the original report quoted above.

On the last day a blood culture was carried out and S. Dubin isolated.

The temperature chart shows a low but persistent pyrexia throughout.

The main point of note about this case is, of course, the prolonged, subacute nature of the illness.

Meningitis due to Coliform Bacilli.

Case 97, E.R., a girl aged seven years, was admitted on the 7th January 1945 with a history of tonsillectomy three weeks previously followed by chicken pox. She continued to complain of earache since the tonsillectomy.

Two days before admission she was taken ill again with headache, shivering and vomiting, with insomnia and anorexia.

On admission she showed typical meningeal signs. Lumbar puncture produced 24 c.c. of opalescent fluid, under pressure, containing increased cells (polymorphs and endothelial cells). The chemistry showed protein 60 mgm per 100 c.c., glucose 57 mgm per 100 c.c. and chlorides 668 mgm per 100 c.c. No organisms were cultured but staphylococci and a coliform organism were seen in direct film and regarded as probable contaminants. The former presumably were, but the latter reappeared in a later sample. Blood culture was sterile but a coliform bacillus was isolated from an abscess which developed on the right shoulder region.
Treatment was with Sulphathiazole 1 Gm intravenously followed by two courses of Sulphathiazole with little apparent effect.

During the following two weeks the temperature gradually tended to settle and the patient was transferred on the forty-ninth day to another hospital where she died later from cerebral abscess.

See skeleton chart for further information.
During the period November 1946 to March 1948 inclusive, six cases of pyogenic meningitis as previously defined were admitted to Rush Green Hospital. Four of these (Cases 98, 100, 102 and 103) were treated in the writer's wards, and the remaining two cases (Cases 99 and 101), admitted to other wards, were examined and kept under observation by the writer.

The six cases included two cases of pneumococcal meningitis, two of meningitis due to haemophilus influenzae, and two of streptococcal meningitis.

The patients suffering from pneumococcal and streptococcal meningitis were treated with sulphonamides and penicillin, and the remaining two with sulphonamides, penicillin and streptomycin.

Five of the six patients recovered.
Case 98  Pneumococcal Meningitis

S.B.T.  Female  Age 7 years.

Admitted 24 March 1947  Day of Disease - 3rd

History:-

Well until 22 March when illness started suddenly with frontal and occipital headache, shivering, sore throat and vomiting. Has vomited daily since.

Complained of vague pains in the region of the left hip on 23 March. Bowels last moved 22 March.

Previous History:- Nil relevant.


General condition fair. Flushed face.

Nausea congested.

Nose - much postnasal mucus. Otherwise nil to note.

Ears - drums normal.

Heart and lungs - nil to note.

Vague pains in region of left hip.


Provisional Diagnosis

The case was at this point regarded as one of pharyngitis.

Treatment and Progress

(N.B. The day of disease is inserted in brackets after the date)

24.3.47.  (3) Sulphamezathine 1.5 Gms statim.

1.0 Gm 4 hrly.

Tabs. Codeine Co. (Veganin) i statim.


Tendon reflexes (Biceps, triceps, supinat knee jerk, ankle jerk) present, equal and active.

No strabismus.
Heart and lungs - no abnormality.
Abdomen - slight tenderness in left iliac fossa.
P.R. faeces - otherwise no abnormality.
Lumbar puncture 11.30 a.m. Local anaesthesia 1% Novocaine.
12 c.c. slightly turbid, greyish fluid, under increased pressure. Queckenstedt's test positive.
Headache almost completely relieved.
Laboratory examination of the fluid showed translucent, colourless fluid with a small deposit of pus on centrifuging.
Cells - 750 cells per c.mm. Polymorphs and Lymphocytes in equal numbers.
Chlorides - 715 mgm per 100 c.c. Sugar-present.
Direct Film (prepared immediately after L.P.)
Scanty Gram positive diplococci present.
Culture No growth. (N.B. Culture media containing p-amino benzoic acid was not available at this time)
Lumbar puncture 5 p.m. Local anaesthesia 1% Novocaine.
4 c.c. similar fluid removed.
20,000 units crystalline penicillin in 2 c.c. saline diluted by withdrawing 2 c.c. C.S.F. into syringe injected intrathecally.
Enema Constipated result.
2 Penicillin in Beeswax and Oil - 125,000 units intramuscularly 12 hrly.

26.3.47. (5) Condition no better. Apathetic.
Flushed and slightly cyanosed.
Lumbar puncture
5 c.c. fluid removed. Much clearer and under very slightly increased pressure.
20,000 units penicillin injected as above.
No complaint of pain on injection.
Laboratory report - Hazy, colourless fluid.
Cells - 143 per c.mm. Lymphocytes 90%
Polymorphs 10%
Sugar normal.
Gram Scanty Gram positive diplococci.

Lumbar puncture
5 c.c. fluid under normal pressure.
Queckenstedt's test positive.
20,000 units penicillin injected as above.
Cells - 7 per c.mm. Lymphocytes 100%
Sugar normal.
Scanty Gram positive diplococci.
No growth on culture.

28.3.47. (7) Improvement continues.

Lumbar puncture
5 c.c. clear fluid, normal pressure.
20,000 units penicillin injected as above.
Cells - 17 per c.mm. Lymphocytes 100%
Sugar normal.
Scanty Gram positive diplococci.
No growth on culture.

RF Sulphamezathine 0.5 Gms 4 hrly.

30.3.47. (9) Clinically normal in every way.

1.4.47. (11) Stop Penicillin. Sulphamezathine 0.5 Gm 4 hrly. except 2 a.m.

2.4.47. (13) Stop Sulphamezathine.

2.4.47. (18) Lumbar Puncture 3 c.c. clear, colourless fluid under normal pressure.
Queckenstedt's test positive.
20,000 units penicillin injected as above.
Cells - 5 per c.mm. Lymphocytes 100%
Sugar normal. Chlorides 750 mgm per 100 c.c.
No organisms on direct film or culture.

14.4.47. (24) Allowed up.

19.4.47. (29) Discharged fit. No residual signs.
Summary of Treatment.

**Sulphamezathine**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Frequency</th>
<th>Duration</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 Gm</td>
<td>statim</td>
<td></td>
<td>1.5 Gms</td>
</tr>
<tr>
<td>1.0 Gm</td>
<td>4 hrly.</td>
<td>for 3 days</td>
<td>22.0 Gms</td>
</tr>
<tr>
<td>0.5 Gm</td>
<td>4 hrly.</td>
<td>for 4 days</td>
<td>12.0 Gms</td>
</tr>
<tr>
<td>0.5 Gm</td>
<td>4 hrly. except 2 a.m.</td>
<td>for 2 days</td>
<td>5.0 Gms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Total Sulphamezathine in 10 days</strong></td>
</tr>
</tbody>
</table>

**Penicillin in Beeswax Oil intramuscularly**

125,000 units 12 hrly. for 7 days - 1,750,000 units

**Penicillin Crystalline** (1,350 units per mgm) **intrathecally**

20,000 units daily for 4 doses - 80,000 units
Case 92  Pneumococcal Meningitis

B.H.  Male  Age 7 weeks.

Admitted 1 February 1948  Day of Disease - 5th

History:
Cough and convulsions since 25 January 1948. Five convulsions during the night of 31 January. No constipation or diarrhoea. Notified as bronchopneumonia. Sulphonamides before admission 0.25 Gm 4 hrly. for 4 doses Total 1.0 Gms.

Previous History: - Nil relevant.

Condition on Admission: - T. 102.6°F P. 140 R. 48

Lumbar Puncture  Local Anaesthesia.
Fluid under markedly increased pressure. Rate of flow increased immediately on crying. Queckenstedt's test briskly positive on the right side, but indefinite on the left side because of crying. 25 c.c. hazy fluid removed. The hazy ground-glass appearance persisted and there was little tendency to deposit. Direct film of the uncentrifuged fluid showed very large numbers of typical Gram positive lanceolate diplococci but very few cells. Cells 247 per c.m.m., predominantly polymorph. Protein 140 mgm per 100 c.c. Chlorides 650 mgm per 100 c.c. Sugar absent.
Culture produced a good growth of pneumococci sensitive to 1 unit of Penicillin and to 5 mgm Sulphamethazine per 100 c.c.
The pneumococcus isolated was found, on typing against Neufeld test antisera, to belong to Group C. Further typing was not carried out.

Diagnosis: Pneumococcal Meningitis secondary to bronchitis.

Treatment and Progress

1.2.48. (5) Sulphamethazine 150 Gm 4 hrly. 6 p.m.
Penicillin 100,000 units 8 hrly for 3 doses then 100,000 units 12 hrly.

2.2.48. (6) Penicillin 20,000 units intrathecally at 12.30 a.m. On this first occasion crystalline Penicillin was not available for intrathecal injection and Penicillin Sodium of a purity of 1,200 units per mgm. was used. During the night the child remained very ill. In the morning the child was pale, drowsy and irritable and later in the day vomited twice. 20,000 units crystalline Penicillin (1600 units per mgm) in 2 c.c. water was injected intrathecally.

3.2.48. (7) Poor day. Cyanosed and pale. Had several screaming fits. Fontanelle bulging in morning, but there was great difficulty in getting the child to take fluids, and the fontanelle was becoming depressed in the evening. The child vomited the midday feed and had several minor convulsions during the day. The eyes were incoordinated and the pupils dilated. The right pupil was larger than the left. Lumbar puncture failed.

4.2.48. (8) Incoordinate movement of the eyes continues. Generally the child appeared slightly better in the morning, but deteriorated again later. L.P. successful after great difficulty. Heavily blood-contaminated fluid under reduced pressure was withdrawn, and 20,000 units Crystalline Penicillin injected intrathecally. The child's general condition deteriorated rapidly, with increasing coma and the child died at 9 p.m. Permission for a postmortem examination was unfortunately not obtained.
Case 100  Meningitis due to Haemophilus Influenzae

C.K.  Female  Age 1 year.
Admitted 4 January 1948  Day of Disease - 30th

History prior to admission to Rush Green Hospital:

This infant was admitted to another hospital on 12.12.47 as a case of bronchopneumonia, having been treated for a period of six days during which she was given about 6 Gms of Sulphadiazine.

12.12.47. (7) The child looked ill, with rapid respirations and some head retraction. The case was provisionally diagnosed as pneumonia with meningism.

Lumbar puncture produced turbid fluid not under obviously increased pressure. Cells 2,600 leucocytes, 100 erythrocytes. Direct film showed scanty Gram negative diplococci. Culture produced small colonies of Gram negative diplococcal forms which were thought to be meningococci.
X-ray chest - Lung fields clear.

Treatment 100,000 units crystalline penicillin intramuscularly.
Sulphapyridine 0.75 Gms statim
0.5 Gms 4 hrly. for 24 hrs., then
Sulphathiazole 0.5 Gms 4 hrly.
Penicillin 25,000 units intramuscularly 4 hrly. for 6 days.

Total Sulphonamide 28 Gms.
Total Penicillin Intrathecally 100,000 units
Intramuscularly 900,000 units

Cells 250 per c.mm. Sterile on culture.

The meningeal signs and respiratory signs subsided during the next few days and the child became almost afebrile. After five or six days the patient became irritable, with very rapid respirations and remittent pyrexia. Leucocyte count 17,600 per c.mm., mainly polymorphs.
Penicillin therapy was recommenced with 25,000 units intramuscularly four hourly until 1,300,000 units had been given. Erythematous areas appeared on the skin and were considered to be a penicillin reaction.


Sulphathiazole 0.5 Gm four hourly. The cough, pyrexia, rapid pulse and respirations persisted. The child remained irritable, resenting movements of the head and sometimes screaming without apparent reason.

2.1.48. (26) Leucocyte count 20,200 per c.mm.

4.1.48. (30) Slight improvement. Respirations have slowed from over 80 per minute to about 40-45. Sulphathiazole to date in second course - 10 Gms.

Condition on transfer to Rush Green Hospital


Lumbar puncture Local Anaesthesia.

Pressure markedly increased. Queckenstedt's test positive. Rate of flow markedly increased on crying. 20 c.c. turbid fluid removed.

Cells 1,080 per c.mm. Polymorphs 70%. Lymphocytes 30%

Direct film: Moderate numbers of slender Gram negative bacilli showing marked pleomorphism.

Culture: H. influenzae grown. The organism was insensitive to 1 and 10 units of Penicillin, partially sensitive to 5 mgm Sulphathiazole. Sensitive to 5 units Streptomycin. The sensitivity tests were done by the cup method. The organism was not typed.
Treatment and Progress

4.1.48. (30) Sulphamezathine 2 Gms statim then 1 Gm four hourly. Penicillin 200,000 units 12 hrly.

5.1.48. (31) Following receipt of preliminary report of finding h. influenzae in the C.S.F. Streptomycin 20,000 units in 2 c.c. was given by intrathecal injection after removal of several c.c. of C.S.F.

(The Streptomycin was the remains of a solution which had already been prepared and partly used in treatment of a case of tuberculous meningitis whose intrathecal injections were discontinued some days previously).

General condition no improvement. Very ill. Has some head retraction.

5.1.48. (32) Head retraction more marked. Irritable. L.P. 10 c.c. cloudy fluid, under much increased pressure, removed. 20,000 units Streptomycin injected intrathecally. The child gave signs of pain when the Streptomycin was injected.

7.1.48. (33) Remains very irritable. Screaming fits during night. L.P. 17 c.c. cloudy fluid, under moderately increased pressure removed. 20,000 units Streptomycin injected. C.S.F. cells 315 per c.mm. Polymorphs 6%. Lymphocytes 94%. Protein 110 mgm per 100 c.c. Chlorides 740 mgm per 100 c.c. Sugar decreased. No organisms found in direct film or culture.

19.1.48. (45) Improvement maintained. Fretful at times.
L.P. 4 c.c. faintly hazy, colourless fluid.
Pressure normal.
Cells. R.b.cs. 80 W.b.cs. 60 per c.mm.
Culture sterile.

22.1.48. (48) Fit of screaming in morning.
Otherwise well.

29.1.48. (55) L.P. 3 c.c. very faintly hazy fluid.
Normal pressure.
Cells. 54 per c.mm. Lymphocytes 100%

6.2.48. (63) L.P. 3 c.c. faintly hazy fluid.
Normal pressure.
Cells. 49 per c.mm. Lymphocytes 98% Polymorphs 2%
Sugar - slight increase. No organisms on direct film or culture.

11.2.48. (68) Haemoglobin 78.6

16.2.48. (73) Clinically very well.
L.P. 6 c.c. almost clear, colourless fluid, under normal pressure. Queckenstedt’s test briskly positive.
Cells. 28 per c.mm. Lymphocytes 100%
Protein 15 mgs per 100 c.c. Sugar - no decrease.

24.2.48. (81) L.P. 5 c.c. clear fluid under normal pressure.
Cells. 14 per c.mm. Lymphocytes 100%
Protein 15 mgm per 100 c.c. Chlorides 760 mgm per 100 c.c. Sugar normal.
No organisms on direct film or culture.


27.2.48. (84) Discharged.
Summary of Penicillin, Streptomycin and Sulphonamide Treatment.

Before admission to Rush Green Hospital

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
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<tr>
<td>Penicillin Intrathecally</td>
<td>100,000 units</td>
</tr>
<tr>
<td>Penicillin Intramuscularly</td>
<td>2,200,000 units</td>
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<tr>
<td>Sulphonamides</td>
<td>37 Gms.</td>
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After admission to Rush Green Hospital

<table>
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<th>Drug</th>
<th>Dosage</th>
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<tr>
<td>Penicillin Subcutaneously</td>
<td>2,600,000 units</td>
</tr>
<tr>
<td>Streptomycin Intrathecally</td>
<td>180,000 units</td>
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<tr>
<td>Sulphamezathine</td>
<td>44 Gms.</td>
</tr>
</tbody>
</table>
Case 101  Meningitis due to Haemophilus Influenzae

T.C.  Male  Age 1 year 2 months.
Admitted 20 February 1948.  Day of Disease - 3rd.

History
Had a "cold" for a few days four weeks ago, but has been fit for three weeks until -
19.2.48. (1) Appeared normal and took breakfast well. Slept in forenoon and was drowsy when wakened for midday meal which he refused. Has been progressively more drowsy and yet restless, but not irritable, since then. Occasional sudden thin cry. He was not constipated. He has refused food and has vomited several times. Parents noticed his head stiff on 20.2.48.

Treatment before Admission
Penicillin 200,000 units 12 hourly for 3 doses since forenoon of 19.2.48. (2)

Previous History
Fell out of bed and cut head on bowl six months ago. No apparent cerebral injury at the time. Bronchitis 4 months ago. Ill 2 - 3 weeks.

Condition on Admission  T. 103.6°F  P. R.
Lumbar puncture  Local Anaesthesia.
Pressure increased. 6 c.c. very turbid fluid removed.
Cells 3,200 per c.mm. Polymorphs 98% Lymphocytes 2%
Protein 80 mgms per 100 c.c. Chlorides 720 mgm per 100 c.c.  Sugar normal.
Direct film.  Moderate numbers of Gram negative pleomorphic bacilli.
Culture.  Haemophilus influenzae grown.

Treatment and Progress
20.2.48. (3) Sulphamezathine 1 Gm 4 hrly.
Penicillin 200,000 units subcutaneously at 2.30pm and 12hrly. from 7 p.m.
Streptomycin 20,000 units in 2c.c. intrathecally daily.
21.2.48. (4) Slept long periods during night. Taking fluids well but vomited twice.
   Drowsy, restless and irritable when roused.
   Neck rigidity marked. Head retraction slight.
   Kernig's sign positive. Contralateral sign positive.
   Limbs held rather stiff.
   Knee jerks exaggerated but no sustained clonus.
   Biceps, triceps and ankle reflexes brisk. No clonus.
   Abdominal reflexes present. Plantar reflexes flexor.
   Pupils moderate size, equal and react rather sluggishly to light.
   No strabismus or ptosis.
   L.P. 20,000 units Streptomycin intrathecally.
   Fluid turbid.

22.2.48. (5) Slight improvement. Fair night.
   Flushed at times. Neck rigidity still marked and limbs stiff.
   Sulphamezathine discontinued.
   L.P. 20,000 units Streptomycin intrathecally.
   Fluid turbid.

   L.P. 20,000 units Streptomycin intrathecally.

24.2.48. (7) L.P. 20,000 units Streptomycin intrathecally. 3 c.c. faintly hazy, colourless fluid.
   Cells. 137, Polymorphs 5% Lymphocytes 95%.
   Protein 65 mgm per 100 c.c. Sugar no decrease.
   No organisms on direct film or culture.
   Temperature elevated in evening. Not so well.
   Flushed and rather drowsy. Very fretful.
   Neck rigidity marked.
   Sulphamezathine 2 Gms at 3 p.m. then 1 Gm 4 hrly.

   Sulphamezathine discontinued. Penicillin discontinued.
   L.P. 20,000 units Streptomycin intrathecally.
   Streptomycin 0.5 Gms intramuscularly 12 hourly from 7 p.m.


   L.P. 20,000 units Streptomycin intrathecally.
L.P. 20,000 units Streptomycin intrathecally.
1.3.48. (13) L.P. 5 c.c. clear, colourless fluid withdrawn.
Cells. 29 per c.mm. Lymphocytes 100%
Protein 25 mgm per 100 c.c. Chlorides 740 mgm per 100 c.c. Sugar normal.
No organisms on direct film or culture.
4.3.48. (16) Streptomycin discontinued.

Summary of Penicillin, Streptomycin and Sulphonamide Treatment

Penicillin subcutaneously 2,600,000 units
Streptomycin intrathecally 160,000 units
Streptomycin intramuscularly 8Gms = 8,000,000 units
Sulphamezathine 15 Gms.
Case 102  Streptococcal Meningitis

E.A.B.  Male  Age 17 years.

Admitted 5 November 1946.  Day of Disease - ? 13th

History: - Well until 4 weeks previously. Started gradually with increasing frontal headaches. 24.10.46. Shivering and aching limbs. 30. & 31.10.46. Vomiting. Constipated since 2.11.46. Sulphamezathine 4.5 Gms before admission.

Previous History: - Nil relevant.


- General condition poor, but lucid and cooperative.
- Neck rigidity marked. Slight head retraction.
- Kernig's sign strongly positive. Brudzinski's head sign doubtful. Contralateral sign positive.
- Abdominal reflexes present. Plantar reflexes flexor.
- Biceps, triceps, supinator, knee and ankle jerks present, equal and unexaggerated.
- Pupils circular, equal and react sluggishly to light. Moderate photophobia. Marked protrusion of both eyes (left more than right), with marked chemosis and venous congestion of conjunctiva, and oedema of eyelids and across bridge of nose.
- Eye movements partly limited by oedema etc., but lateral movement of both eyes is lost.
- Ophthalmoscopic examination - venous congestion and moderate papilloedema.
- Tender over left frontal sinus.
- Ears normal. Throat slightly congested. No cervical adenitis.
- Pulse soft and poor quality but regular. General examination otherwise negative.

Lumbar puncture  Local Anaesthesia 1% Novocaine. 5 c.c. hazy fluid under slightly increased pressure. 157 cells per c.mm. Predominantly polymorphonuclear. Direct Film (prepared immediately) A very large number of Gram positive cocci, mostly in short chains. Culture failed to grow.
Provisional Diagnosis
Streptococcal Meningitis.
Frontal Sinusitis.
Bilateral Cavernous Sinus Thrombosis.

Treatment and Progress

5.11.46. (13) Sulphamezathine 2.0 Gms. statim.
then 1.0 Gm 4 hrly.

X-ray Sinuses - Appearances were as follows:
- Left frontal sinus - Acute infection. No osteitis.
- Left antrum - Fluid or multiple polypi.
- Right antrum - Chronic hyperplastic sinusitis.
- Left anterior ethmoidal sinus - Opaque.

5.30 p.m. Penicillin Oil 250,000 units intramuscularly.
6.20 p.m. Camopen gr. 1/3 Scopolamine gr. 1/150 subcutaneously.
7 p.m. Operation. General Anaesthetic (Gas, Oxygen, Ether).
Left external frontal sinusotomy. Pus not under pressure. Left intranasal maxillary sinusotomy.
No pus.
12 m.m. Penicillin in Oil 250,000 units intramuscularly.

6.11.46. (14) Restless night in spite of Taps.
Codeine Co. ii at 2 a.m.
7 a.m. Penicillin in Oil 500,000 units intramuscularly 12 hourly.
Proptosis remains marked. Little change in general condition. Remains lucid and cooperative. Taking fluids well.


Penicillin in Oil 250,000 units intramuscularly 12hrly.

9.11.46. (17) Not quite so well. Colour still poor.
Penicillin in Oil 500,000 units intramuscularly 12hrly.
10.11.46. (18) Photophobia still well marked, especially left eye. Slight increase in proptosis left side. Taking light diet.

11.11.46. (19) Definite improvement. Antrum washout clear. Right eye almost back to normal. Lateral rectus acting. Proptosis still marked in left eye. Meningeal signs have subsided.

13.11.46. (21) Sulphamezathine 0.75 Gms. 4 hourly.


15.11.46. (23) Remains pyrexial, possibly due to Sulphonamides. Faint sulphonamide or penicillin rash on trunk. Penicillin discontinued.

16.11.46. (24) Sulphamezathine discontinued.


29.11.46. (37) Symptom free. General condition good. Wound well healed. Allowed up.

11.12.46. (49) Fit. No meningeal signs. Only remaining sign of thrombosis is slight dilatation of veins of left lateral conjunctiva. Discharged.

Summary of Sulphonamide and Penicillin Treatment

<table>
<thead>
<tr>
<th>Sulphamezathine by mouth</th>
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<tbody>
<tr>
<td>Pre-admission in 1 day</td>
</tr>
<tr>
<td>2 Gms statin</td>
</tr>
<tr>
<td>1 Gm 4 hrly. for 8 days</td>
</tr>
<tr>
<td>2 Gm 4 hrly. for 3 days</td>
</tr>
<tr>
<td>Total Sulphamezathine in 12 days</td>
</tr>
</tbody>
</table>
Penicillin in Oil intramuscularly.

250,000 units 2 doses on 5.11.46. 500,000 units
500,000 units 12 hrly. for 2½ days 2,500,000 units
250,000 units 12 hrly. for 1 day 500,000 units
500,000 units 12 hrly. for 6 days 6,000,000 units

Total Penicillin in 10 days 9,500,000 units

12.2.46. Follow-up. Seen as outpatient.
Was well for more than six months, but since
leading a more strenuous life in the Army during
the past six months has had occasional feelings of
faintness, and a few days ago complained of
transient blindness in the right eye.

Examination reveals no abnormality except slight
sluggishness of the right pupillary light reflex
as compared with the left. Eye movements are
normal.
Case 103

Streptococcal Meningitis.

J.F.B. Male Age 9 months

Admitted 16 December 1947. Day of Disease - 5th

History:-
Well until 12.12.47 when the child became irritable and off colour. A scarlatiniform rash appeared on the same day but had disappeared two days later.
The child vomited on 13 and 14.12.47.
Last bowel action 14.12.47.

Previous History:-
No relevant history known. Child was adopted when 4 months old. The foster parent's attention was drawn at the time to the large size of the infant's head and anterior fontanelle.

Condition on Admission T. 970 P. 144. R. 40.

1 p.m. Infant ill and pale. Large square head and very large anterior fontanelle which is not bulging. Respirations rapid but no signs of consolidation. Fauces injected only.

Sulphanezathine 1 Gm 4 hourly.
Mist. Tuss. Infant 1 fl. dr. 4 hourly.

Treatment and Progress

16.12.47. (5)

6.45 p.m. General condition deteriorated. Drowsy and apathetic. Eyes sunken and half closed. Pulse fairly good quality and regular.
Respirations not unduly rapid or distressed.
Nikethamide 1 c.c. injected intramuscularly.
Occasional thin cry.
No neck rigidity. No head retraction. Fontanelle neither bulging nor depressed.
Kernig's sign negative. Brudzinski's head sign and contralateral sign negative.
Knee jerks and ankle jerks positive and equal.
Abdominal reflexes present. Plantar reflexes flexor. Pupils moderate size, circular, equal, react sluggishly to light.
Ears - drums normal.
66.

Lumbar puncture. Local Anaesthesia. 1% Novocaine.
20 c.c. slightly turbid fluid under slightly increased pressure.
Cells. 980 per c.mm. Predominantly polymorphs.
Chlorides 750 mgm per 100 c.c. Protein 30 mgm per 100 c.c. Sugar decreased.
Direct Film prepared immediately. Gram positive cocci in pairs and chains. Some intracellular.
Culture. Organisms resembling streptococci were grown in the primary broth culture with para-amino benzoic acid. Further attempts to isolate the organisms failed.

12 mn. 10,000 units Crystalline Penicillin (1,600 units per mgm) in 5 c.c. water by intrathecal injection after removal of an equivalent amount of fluid.

17.12.47. (6) 1 a.m. 200,000 units of Penicillin in 2 c.c. water subcutaneously.
8 a.m. 200,000 units Penicillin subcutaneously 12 hrly.

Neck rigidity marked. Reluctant to take feeds.

18.12.47. (7) Still very ill. Eyes vacant and sunken.
Respirations rapid but not distressed. Mast.Tussis discontinued. Twitching of right arm, neck, mouth and check in evening.

19.12.47. (8) Attack of sharp crying during night.
Flushed. Slight improvement, but still fretful. Vomited 2 p.m. feed.

20.12.47. (9) Feeds taken well. Sulphamezathine discontinued. Right arm feels stiff and painful and is not used.


27.12.47. (16) Lumbar puncture 10 c.c. hazy, colourless fluid under normal pressure removed. Cells 134 per c.mm. Lymphocytes 100%. Chlorides 760 mgm per 100 c.c. Protein 30 mgm per 100 c.c. Sugar some decrease. No organisms seen in direct film or culture.


30.12.47. (19) Improved generally.

1.1.48. (21) Vomited in morning. No meningeal signs. Lumbar puncture 3 c.c. faintly hazy, colourless fluid. Pressure normal. Queckenstedt test positive bilaterally. Cells. 142 per c.mm. Polymorphs 6% Lymphocytes 94%. Protein 30 mgm per 100 c.c. Sugar normal. Chlorides 760 mgm per 100 c.c. No organisms seen in direct film or culture.

3.1.48. (23) Teething - both lateral upper incisors erupting. This probably accounts on part for fretfulness recently. Right arm still used very little but there is some voluntary movement of all muscle groups. No weakness elsewhere on right side. Tendon reflexes slightly exaggerated in right arm.

8.1.48. (28) X-ray skull shows no evidence of hydrocephalus.


20.1.48. (40) Lumbar puncture 5 c.c. clear, colourless fluid. Pressure normal. Cells. 4 per c.mm. Lymphocytes 100%. Protein 25 mgm per 100 c.c. Chlorides 760 per 100 c.c. Sugar normal. No organisms in direct film or culture.

25.1.48. (45) No meningeal signs. Weakness of right arm remains, but less marked. Discharged.
Summary of Sulphamezathine and Penicillin Treatment

Sulphamezathine 1.0 Gm 4hrly.
   for 4 days = 24 Gms
Penicillin Crystalline by
   intrathecal injection 1 dose = 10,000 units
Penicillin 200,000 units
   in water subcutaneously
   12 hrly. for 9 days = 3,600,000 units

Follow-up

3.2.48. (54) Considerable improvement in range and
   power of movements of right arm, but still has
   well marked weakness of flexors of fingers.
PART III - DISCUSSION.

The primary object of this paper was originally to discuss the effects of various forms of treatment of the different types of pyogenic meningitis. It soon became evident, however, that a discussion on this subject alone would be relatively unfruitful if the equally important problem of early diagnosis were not considered at the same time.

As the figures in this and many other series show, the problem of differential diagnosis between meningococcal meningitis and the other types of meningitis was, from the point of view of the treatment of the case of little more than academic interest before the advent of sulphonamides. If the case were treated as one of meningococcal meningitis the treatment given would be the best available if the diagnosis proved to be correct. If on the other hand the case later proved to be a pneumococcal meningitis or a tuberculous meningitis, the physician's sole consolation was that the almost inevitably fatal outcome could not have been averted by any means at his disposal.

The situation is now considerably different since the introduction of the sulphonamides and the antibiotics. On the one hand, treatment which may be adequate for meningococcal meningitis
may be quite inadequate for other forms of meningitis. On the other hand the more vigorous treatment accorded to the non-meningococcal forms would, if applied to all cases of meningitis as a routine, give rise to unnecessary discomfort or even danger to patients suffering from the meningococcal form of the disease.

The writer proposes therefore, to discuss some of the points which must be borne in mind when confronted with a patient presenting meningitic symptoms.

Before attempting to draw conclusions from the findings in the present series of cases, a number of points must be borne clearly in mind.

The first, and in some respects most important point is that all the cases concerned in the series were patients in an isolation hospital. Every case, therefore, was admitted to hospital as a case of infectious disease (usually as meningococcal meningitis). As the pyogenic meningitides are not, in the usual sense of the word infectious diseases, and are certainly not notifiable diseases, it follows that most of the cases fall into three main groups:

(a) those which so resembled meningococcal meningitis that an erroneous diagnosis of that disease was made,

(b) those incorrectly diagnosed and notified as some other disease, e.g. pneumonia and
(c) those who were admitted suffering from a notifiable infectious disease, and developed meningitis as a complication. It follows therefore, that the cases in the series do not form a true cross section of meningitis as occurring in this country. It would accordingly be unwise to draw too firm conclusions from the figures and analyses compiled from them. This caution is reinforced by the fact that the number of cases in the series is of necessity relatively small. The incidence of the non-meningococcal, non-tuberculous forms of meningitis is relatively so small that few centres and few clinicians in this country outside special centres (e.g. head injuries hospitals) have a vast experience of these forms of meningitis. The literature deals in great part with single cases and small series, or analyses of cases which have been admitted to a particular hospital over a period of years.

Part I of this paper suffers from the defect inherent in small series that the same term as used by different observers may have different meanings or at least different shades or degrees of the same meaning. INCIDENCE.

This is a subject in which may of the points can most easily be demonstrated by the comparison of graphs and tables.
There is no generally available basis for estimating the case incidence in the country as a whole, as the pyogenic meningitides are not notifiable, nor are they centrally recorded in any other way. Notifications are in any case notoriously inaccurate, based as they are on early provisional diagnosis of the case. This is rapidly demonstrated by the fact that all except a few of the present series were in fact notified as meningococcal meningitis.

One might expect the total death rates to be of some assistance in the presulphonamide period since it is generally agreed, as will be discussed later, that pyogenic meningitis was at that time almost invariably fatal. The total deaths must, therefore, closely approximate the case incidence during this period. Since the advent of sulphonamides it is no longer possible to draw any close parallel between the number of deaths and the case incidence even by working back from other published case mortality rates, since these again do not usually give a true picture of the overall case mortality throughout the country. Human nature being what it is, an observer is more likely to publish figures and results if these are above average than if they are below average.
Returning to the figures relating to deaths, the Annual Report of the Registrar-General for Scotland adopts the classification given in the International Long List of Causes of Death, which groups meningitis other than meningococcal and tuberculous meningitis under the heading "Meningitis (not meningococcal)". This classification is adopted by the Medical Research Council's "A Provisional Classification of Diseases and Injuries for Use in Compiling Morbidity Statistics" which includes "aseptic meningitis; basic pneumococcal meningitis; cerebral meningitis; cerebro-spinal arachnitis or arachnoiditis; cerebro-spinal inflammation; chronic cerebrospinal meningitis; encephalomeningitis; haemorrhagic pachymeningitis; leptomeningitis; meningitis (unqualified); meningitis serosa circumscripta; meningomyelitis; pachymeningitis; pneumococcal, purulent, septic, serous, spinal, staphylococcal, streptococcal or suppurative meningitis; pneumococcal or streptococcal cerebro-spinal meningitis; spinal pachymeningitis".

It is obvious that this heterogeneous miscellany provides a relatively poor basis for analysis of figures, and that only the broadest comparisons can be made.
The last quoted publication includes this group under M.R.C. code No. 305, but provides a fifth column figure code to differentiate among the various causal organisms, as follows:—

--- 0 Infections due to a streptococcus
--- 1 Infections due to a pneumococcus
--- 2 Infections due to a staphylococcus
--- 3 Infections due to other identified cocci
  (except those specified in Section A)
--- 4 Infections due to Bact. coli
--- 5 Infections due to other identified bacilli
  (except those specified in Section A)
--- 6 Infections due to other identified infective agents (except those specified in Section A)

(Section A covers Infective and Parasitic Diseases and includes headings for Meningococcal and Tuberculous Meningitis).

Thus Streptococcal and Pneumococcal Meningitis would be coded under 305-0 and 305-1 respectively, while meningitis due to haemophilus influenzae would be included under the less precisely defined heading "305-5 - Meningitis due to other identified bacilli".

Should this or a similar coding system come into general use, morbidity and mortality statistics in relation to these various forms of meningitis would become more accurate and correspondingly more valuable. At present, however, one must rest
content with the all-embracing heading "Meningitis (other than Meningococcal)". Henceforth the term "Non-meningococcal Meningitis" will be used in this paper to imply this group, in order to avoid the repetition of the phrase "Meningitis other than Meningococcal and Tuberculous Meningitis".

Annual Incidence.

Appendix I demonstrates that relatively few cases of pyogenic meningitis were admitted to Edinburgh City Hospital each year during the twenty years prior to 1940, but that a relatively larger number was admitted during the two World Wars. During both these periods the incidence of Meningococcal Meningitis was also high (see Appendix 12) and it appears at first sight that an increase of Meningococcal Meningitis is accompanied by an increase in pyogenic meningitis. However, Appendix II demonstrates that the incidence of "Meningitis (other than Meningococcal)" in Scotland as a whole does not show a correspondingly large increase during 1940-1943. Although the figures for 1940 and 1941 are slightly above those for 1939, it is reasonable to suppose that
the number of cases of meningitis vaguely certified, and thus of necessity classified under the miscellaneous group, was slightly raised. On the figures available in respect of Scotland as a whole it is not justifiable to argue that an epidemic of meningococcal meningitis is accompanied by any marked increase in the non-meningococcal form. Furthermore the number of deaths due to pyogenic meningitis occurring in Edinburgh City Hospital does not correspond in any demonstrable way with the incidence in Scotland as a whole. Whereas non-meningococcal meningitis in Scotland shows a general downward trend during the period 1931-1945, the numbers of deaths in Edinburgh City Hospital due to pyogenic meningitis show the considerable increase in 1940 onwards which has already been noted. As the majority of the admissions to Edinburgh City Hospital are from Midlothian (including Edinburgh Burgh) a comparison was made between the deaths due to non-meningococcal meningitis in Midlothian, and deaths due to pyogenic meningitis in Edinburgh City Hospital (Appendix II). It will be seen that the Midlothian
deaths remain fairly steadily in the neighbourhood of 20 deaths annually until 1944-5 when the figure is approximately halved and show neither the marked downward trend shown in the figures for the whole country, nor the rise in the War years shown by the City Hospital figures. The graph shows that deaths due to pyogenic meningitis in the City Hospital form only 11.4% of the total deaths in Midlothian due to Non-meningococcal meningitis during the period 1931 to 1939 inclusive, but that the figure rises to 48% in the period 1940 to 1945 inclusive. It is apparent, therefore, that a higher proportion of all cases of non-meningococcal meningitis was being admitted to the City Hospital rather than to other hospitals (e.g. Sick Childrens Hospital) most being provisionally diagnosed as meningococcal meningitis, due mainly to the fact that the epidemic of the latter disease kept it in the forefront of the clinicians mind.

The explanation of the gradual drop in fatalities in Scotland as a whole is not obvious without breaking down the figures further, to separate the cases of proved pyogenic meningitis from the vaguely described
remainder. The relative incidence of the different types of pyogenic meningitis varies considerably in different published series.

North, Wilson, and Anderson (1946) reproduce several sets of figures from American, Canadian and Australian sources. The figures are reproduced in Appendix 18. It will be seen that, excluding tuberculous and meningococcal meningitis, the overall figures show pneumococcal meningitis to be the commonest, followed closely by influenzal and then streptococcal, with staphylococcal a very bad fourth. The value of such figures is once more of doubtful value. It will be noticed that the figures from the New York Department of Health Bureau of Laboratories show a marked preponderance of pneumococcal and streptococcal meningitis over influenzal meningitis, which is commonest in all the other series.

Huntingdon and Wilkes Weiss (1936) from St. Louis produce another series in which influenzal meningitis is less common than streptococcal or pneumococcal meningitis.

All the above are from children's hospitals, so that possibly undue emphasis falls on pneumococcal and
particularly on influenzal meningitis. Savitsky (1944) gives the order of frequency of non-
meningococcal non-tuberculous meningitis as pneumo-
coccal, streptococcal, influenzal and staphylococcal, 
with the proviso that influenzal meningitis is the 
commonest form in children under two years of age. 
He then goes on to list over thirty other organisms 
which have on occasion been reported to cause 
meningitis.

Hayes (1940) referring to statistics from both 
sides of the Atlantic, that influenzal meningitis 
ranks third or fourth among the purulent meningitides, 
while Mutch states that this disease is commoner in 
America and suggests that the general resistance to 
haemophilus influenzae infections in this country is 
due to the prevalence of the common cold.

The crux of the matter is that after meningococcal 
and tuberculous meningitis, the three commonest 
causal organisms are pneumococci, streptococci and 
haemophilus influenzae. Following these but a long 
way behind is the staphylococcus. PS. pyocyanae 
accounts for some of the cases of meningitis following 
spinal anaesthesia, and a large number of other
organisms have been known on rare occasions to produce meningitis.

Seasonal Incidence.

The City Hospital figures shown in Appendix 3 are too small to speak for themselves, but as can be seen in Appendix 13, they do not conflict with the figures for non-meningococcal meningitis for Scotland as a whole which show a flat summit in March and April, the minimum figure in August being a little less than two thirds of the maximum. The curve is more gentle than that seen in Meningococcal Meningitis where the peak is about a month earlier and the minimum figure is little more than one third of the maximum. Tuberculous meningitis has a later maximum and minimum, the latter being a little over half the peak figure. In Lobar Pneumonia, Scarlet Fever and Influenza, the peak is in January and the minimum figure in the early autumn. Deaths from Otitis media and Diseases of the Ear and from Mastoid Disease show curves which bear a considerable resemblance to that of non-meningococcal meningitis. Thus the seasonal incidence of non-meningococcal meningitis corresponds in general with that of many other airborne bacterial infections but the peak tends to be later than that found in lobar pneumonia.
On the question of seasonal incidence Straker, Hill and Lovell (1939) in their report for the Ministry of Health on a study of the Nasopharyngeal Bacterial Flora of persons in South East England, show the following quarterly percentage carrier rates for personnel at the London School of Hygiene and Tropical Medicine during the years 1930 to 1937:

<table>
<thead>
<tr>
<th>Quarter</th>
<th>Pneumococcus</th>
<th>Haemolytic Strept.</th>
<th>M. Influenzae</th>
<th>Meningococcus</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>NP</td>
<td>N</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>1</td>
<td>31.4</td>
<td>11.9</td>
<td>66.9</td>
<td>9.8</td>
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<tr>
<td>2</td>
<td>29.6</td>
<td>9.0</td>
<td>64.7</td>
<td>9.0</td>
</tr>
<tr>
<td>3</td>
<td>22.6</td>
<td>3.1</td>
<td>60.5</td>
<td>3.8</td>
</tr>
<tr>
<td>4</td>
<td>32.3</td>
<td>8.7</td>
<td>61.3</td>
<td>4.3</td>
</tr>
</tbody>
</table>

(NP - Nasopharynx  N - Nose)

The nasal carrier rates for haemolytic streptococci and meningococci were so small that comparison was not possible. It will be seen that in very general terms these carrier rates agree with the seasonal incidence of nonmeningococcal meningitis shown in Appendix 13, although the meningitis curve appears to be rather later. Whether this may be due to enhancement of virulence towards the end of the period of increased carrier rates, by passage, is at present a matter for conjecture.

In particular reference to haemophilus influenzae Straker, Hill and Lovell found no well-marked correlation between influenza epidemics and increased nasal of nasopharyngeal carrier rates.
Age/Sex Incidence.

The City Hospital figures of age distribution, shown in the form of a chart in Appendix 4, show certain marked differences between types as will be discussed shortly. The overall figures for Pyogenic Meningitis at the City Hospital shown in Appendices 4 and 14 demonstrate the general definite preponderance of males over females in most age groups. The figures for Nonmeningoocccal Meningitis in Scotland as a whole shows a similar but less marked disproportion as Appendix 14 demonstrates. Meningococcal Meningitis exhibits the same tendency except in the 10-15 year old age group, and in some of the oldest age groups. Moreover, as shown in Appendix 16, the male death rates for all causes are greater than the female death rates throughout the age groups, so that it is not enough merely to record the fact that more males than females succumb to pyogenic meningitis. Appendix 17 compares the relationship between male and female deaths (not death rates) from All Causes and from Nonmeningoocccal Meningitis. From this it will be seen that the preponderance of males is on the whole greater in the latter than in the former group. The City Hospital figures in the first four age groups show an even more marked disparity. After fifteen years of age the figures are
too small to be worthy of discussing by five year age groups and must be compared as a whole. The total male deaths from all causes in Scotland during the period 1931 to 1946 inclusive were 204,936, while the female deaths were 8.8 per cent less at 186,602. The female deaths in Scotland under the heading Meningitis (other than Meningococcal) were 1,428 or 19.4% less than the male deaths (1769). The female deaths in Edinburgh City Hospital due to pyrogenic meningitis during the same period were 19, or 61.2 per cent less than the 1,729 deaths among males. It is obvious therefore that pyrogenic meningitis contributes considerably more than its fair proportion to the preponderance of male over female deaths due to all causes.

The age distribution shows that the highest numbers of cases and deaths occur in the first year of life and that the next four years claim a large proportion of the remainder. This tendency is particularly pronounced in "Influenzal Meningitis" as the City Hospital figures show (Appendix 4B). Fortyeight per cent of the cases occurred in infants under twelve months of age (36% between 6 months and 1 year), and only twelve per cent were over four years of age. The reason will be discussed later. In pneumococcal meningitis slightly older children are affected. Fifteen per cent were under one year, and just over half the cases were under ten years old.
Streptococcal meningitis is spread fairly evenly over the age groups.

Fothergill and Wright (1933) give an explanation for the age distribution and high fatality rates of influenza meningitis in the first three years of life with the exception of the first few months. Using defibrinated whole blood, they demonstrated that blood taken from newborn infants and infants under two months of age has considerable bactericidal powers for Haemophilus influenzae. After this the blood of infants between the ages of two months and three years with few exceptions show practically no bactericidal powers. Later, the bactericidal properties are increasingly in evidence, and all adult sera tested were actively bactericidal. This corresponds in principle with the relative immunity to diphtheria in children under one year of age, and the later gradual development of acquired immunity due to repeated exposure to subinfective doses of diphtheria bacilli. The fading of what is virtually passive immunity passed on from the mother is more rapid in the case of Haemophilus influenzae.
as is the subsequent development of active partial immunity. Straker, Hill and Lovell's carrier rate figures already quoted give an indication of the frequency of exposure to this organism.

In regard to sex distribution this same report records that more males than females were nasopharyngeal carriers of pneumococci and haemolytic streptococci, but it is not recorded whether the environmental circumstances of males and females were comparable. The figures for H.influenzae show a similar but less marked trend and are regarded as inconclusive.

It is a well known and generally accepted fact that the general death rate among males is greater than among females with the possible exception of the period of maximum child-bearing, but the reason for the relative fragility of male children remains obscure.
There is general agreement that the signs of the various types of meningitis are on the whole similar, and it is a fact that it is rarely possible to forecast with certainty the type of meningitis present in any case. A detailed analysis of large numbers of cases may demonstrate that one particular sign or feature is commoner in one type of meningitis than in another, but such knowledge is of little more than academic interest when confronted with an individual patient. In the writer's opinion the two essential points to be kept in mind are; first, that all cases of meningitis do not produce the typical textbook description including neck rigidity and positive Kernig's sign; and second, that there are relatively common types of meningitis other than meningococcal and tuberculous, even in the absence of an obvious primary focus.

Before passing to the consideration of the signs themselves, routes of infection must be considered, and to this end the anatomical and physiological factors involved have to be borne in mind.

The dense fibrous dura mater encephali consists of two layers, the outer layer acting as the periosteal covering of the inner surface of the cranial bones, and becoming continuous with the periosteum covering the exterior of the cranial bones at the foramen magnum, the various foramina through which nerves and bloodvessels pass, and, before closure
of the sutures and fontanelles, via the thin layer of fibrous tissue persisting between the bone edges in the suture lines. The outer surface of the dura is bound down to the cranial bones by fine fibrous processes and extensions around bloodvessels, just as normal periosteum is bound down to bone. Except along the suture lines and on the floor of the cranial cavity there are small lymph spaces (the epidural spaces) which provide a plane of cleavage between this outer dural layer and the cranial bones and across which the fibres already mentioned pass. The lymphatics draining this epidural space pass to the superior deep cervical lymph glands. Part of the venous drainage from the cranial bones passes into the meningeal veins and part into adjacent venous sinuses.

The inner layer of dura mater is largely applied to the inner surface of the outer layer but is reflected from the supporting falx cerebri, falx cerebelli and tentorium cerebelli. This inner dural layer supplies a closely investing sheath which becomes continuous with the fibrous sheath of nerves or vessels leaving or entering the cranial cavity. At the point of exit the two layers of dura are closely bound together.
In the angles of reflexion, and thus between two layers of dura, lie the venous sinuses, which together with the meningeal veins, provide the venous drainage of the brain and structures in the cranial cavity, and to some extent of neighbouring extra-dural structures. Somewhat different in formation are the two cavernous sinuses, lying on either side of the sella turcica, lying between the two layers of dura, roofed over by the inner layer, but subdivided by numerous fibrous stands and having several important structures embedded in its lateral walls, namely the third and fourth cranial nerves, and the ophthalmic division of the fifth, while the sixth cranial nerve and the internal carotid artery with its surrounding sympathetic plexus pass through the cavity of the sinus rather than in its wall.

The cavernous sinuses receive blood from the orbit, the frontal and anterior ethmoidal sinuses and the roof of the nose via the ophthalmic veins; from the dura overlying the lesser wing of sphenoid and adjoining parts, including the underlying bone, via the sphenoparietal sinus, and from the inferior cerebral veins. The two cavernous sinuses are connected in front of and behind the hypophysis by
the anterior and posterior intercavernous sinuses, and has several venous communications. Those which concern us here are the communications via the superior ophthalmic vein and supraorbital vein with the frontal diploic vein, which drains the anterior part of the frontal bone; second, via an emissary vein, with the pterygoid plexus which drains the deep structures of the face including both alveolar canals, the mucous lining of the maxillary antrum and the infra orbital region. Another inconstant emissary vein joins up with the veins in the facial canal.

In addition to receiving blood from the brain and meninges the remaining sinuses receive tributaries from the diploic veins, while there are several emissary veins which normally convey blood from the sinuses to the exterior of the skull, communicating also with the diploic veins between the tables of the cranial bones. Apart from those already mentioned in connection with the cavernous sinus one other is worthy of note. This is the frontal emissary vein which, in the child and sometimes in the adult joins the end of the superior sagittal sinus and the veins of the frontal sinus in the roof of the nasal cavity or the angular veins.

Structures of present importance which lie in close relation to the external surface are as follows:
The frontal sinuses are separated from dura only by the thin inner table of the frontal bone in the anterior part of the anterior fossa.

The sphenoidal sinus underlies the tuberculum sellae in front of the hypophyseal fossa, and is in similar relation to the cavernous sinuses at the side.

The roof of the nasal cavity is formed by the cribriform plate of ethmoid, which is pierced by the filaments of the ophthalmic nerve.

The orbit is roofed over by the thin orbital plate of frontal, but also communicates with the cranial cavity principally through the superior orbital fissure.

The medial part of the orbital plate of frontal roofs over the posterior ethmoidal cells.

Turning to the ear, the tympanic cavity and antrum are separated from the middle fossa of skull by the thin tegmen tympani which forms part of the anterior surface of the body of petrous temporal, while the mastoid air cells are in close proximity to the sigmoid portion of the lateral sinus. The superior semicircular canal underlies the arcuate eminence on the petrous temporal, while the cochlea and vestibule are in close apposition to the depths
of the internal auditory meatus. The labyrinthine perilymphatic space communicates via the cochlear aqueduct with the subarachnoid space, and the endolymphatic space opens into the ductus endolymphaticus which terminates under the dura in communication with the epidural space.

The pia mater is extremely delicate and closely invests the surface of the brain tissue following every irregularity and providing sheaths for the fine bloodvessels entering the brain substance. An extension of the subarachnoid space accompanies the vessels some distance into the brain substance.

The arachnoid, however, spans the sulci and irregularities with the exception of the central and lateral fissures. Between the dura and arachnoid lies the subdural space, the surfaces being lined with endothelium and closely applied to each other.

The space between arachnoid and pia mater is filled with cerebrospinal fluid. As the arachnoid bridges irregularities which pia mater follows, there is left between the two a variable space in which is a meshwork of filaments binding the two loosely together. The two are fairly closely applied, one to another over the cerebral and cerebellar hemispheres.
but the irregularities of the base provide various spaces or cisterns where the meshwork is less in evidence. Some of these are named and of some importance in meningitis. The cisterna magna (cisterna cerebellomedullaris) lies between the under surface of cerebellum and the posterior surface of the medulla, and can be reached by a needle passing through foramen magnum between the occiput and atlas. Passing round the sides of medulla to the under surface of pons we come to cisterna fontis, in front of which lies the interpeduncular cistern between the temporal lobes. Further forward still lies a cistern in front of the optic chiasma. Thus a series of freely communicating spaces cover most of the central part of the base of the brain.

The arachnoid provides a sheath which runs a short distance along the beginnings of the nerves before fading out. The subarachnoid space itself is also carried for a little distance along the nerves and there is some connection between the subarachnoid space and the lymphatic channels of the nerves. The importance of this in regard to the olfactory nerves requires no emphasis.

Through the subarachnoid space run the larger vessels, and an invagination of pia mater passes into
the interior of the brain between the splenium of corpus callosum above and the corpora quadrigemina below, coming to lie across both thalami and the endothelial roof of the third ventricle, and under the endothelium ling the floor of the lateral ventricles. In the margins of this invagination and of two fringes passing from the under surface into the cavity of the third ventricle, lie plexuses of veins, the choroid plexuses respectively of the lateral and third ventricles. A similar invagination passes in from the pia mater along the roof of the lower part of the fourth ventricle, and in this lies the choroid plexus of the fourth ventricle. The veins of the choroid plexuses are thus separated from the cavity of the ventricles by two thin membranes, namely the pia mater and the ependymal lining of the ventricles.

The coverings of the spinal cord are similar in general to those of the brain but there are several important differences.

The external layer of dura is absent, being replaced by the periosteum of the vertebrae and the intervening posterior longitudinal ligament in front and ligamenta flava behind. These are continuous at the foramen magnum with the outer layer of dura, via the membrana tectoria and posterior atlanto-occipital membranes respectively. The inner layer
of dura becomes continuous with the spinal dura at the foramen magnum and forms a tube which extends down to the level of the second or third section of sacrum where it contracts to form the filum terminale which passes through the sacral canal to be firmly anchored to the back of the coccyx. The spinal dura is thus fixed firmly at top and bottom but loosely throughout its length, since a plexus of veins lies between it and the walls of the spinal canal (i.e. in the peri-dural space, e.g. the cranial blood sinuses), while a few fibres attach it loosely to the backs of the bodies of the vertebrae.

The pia mater spinalis is tougher than that of the brain and helps to support the cord. Laterally the fibrous band of the denticulate ligament originates between the anterior and posterior nerve roots, to be attached to the inner surface of the dural tube at a series of approximately twenty points, thus slinging the cord safely but loosely in the centre of the space. The arachnoid, continuous with that covering the brain, lies in contact with the dura, with the subdural space between them, and the subarachnoid space between arachnoid and pia. The contents of the spinal theca are small in relation to the diameter of the tube. During development the growth of the spinal cord lags behind that of the vertebral column, so that the spinal nerves have a progressively longer and more oblique path within the spinal canal before
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emerging at the intervertebral foramina, and the end of the cord itself lies opposite the body of the first lumbar vertebra. Below this point the dural tube or spinal theca therefore contains the proximal part of the lumbar and sacral nerves, each with their investing coverings of pia, the whole forming the cauda equina. The pial covering of the end of the cord shrinks to a thread which passes down as the filum terminals to be joined lower down by the end of the dura and arachnoid as described already.

The formation and disposal of cerebrospinal fluid may with advantage be considered at this point.

The choroid plexuses of the third and lateral ventricles receive their blood supply from the anterior choroidal branches which come off near the termination of the internal carotid artery, and from the posterior choroidal branches of the posterior cerebral arteries, while the choroid plexus of the fourth ventricle is supplied from the posterior inferior cerebellar branches of the vertebral arteries. The plexuses are drained by choroid veins from which the blood passes via the internal cerebral veins, which join to form the great cerebral vein, which enters the anterior end of the
straight sinus, which in its turn passes the blood to the transverse sinuses and thence to the internal jugular vein.

The pressure in the choroid plexus is presumed to be such that the opposing osmotic tension is overcome and by a process of selective filtration a watery fluid normally containing little more than the crystallloid elements of blood is produced and passed into the ventricles of the brain. From the lateral ventricles the cerebrospinal fluid passes through the interventricular foramina into the third ventricle and thence via the cerebral aqueduct to the fourth ventricle, from which the excess passes to the subarachnoid space by way of the median and lateral apertures (foramina of Magendie and Luschka) in the lower part of the roof and extrémités of the lateral recesses of the fourth ventricle, while a certain small proportion passes into the central canal of the spinal cord.

In the subarachnoid spaces the cerebrospinal fluid diffuses over the surface of the brain and down the spinal subarachnoid space. It will be understood from the description of the cisterns that the flow there is almost unimpeded but that the closer apposition of the pia and arachnoid over the
hemispheres causes some slowing of the flow. The fluid is removed from the subarachnoid space by absorption into the venous sinuses from the arachnoid villi, which are small herniations of arachnoid and subarachnoid space into the walls of the sinuses, the "hernia" being covered by a thinned out layer of dura. Samson Wright suggests that important absorption of cerebrospinal fluid is effected by the spinal veins also and also that possibly some passes into the perivascular spaces.

The characters of cerebrospinal fluid which are normally estimated for diagnostic purposes are pressure, turbidity, colour, clot formation, cells, protein, glucose and chloride content, and presence or absence of organisms.

The pressure may be estimated by manometer but this is inconvenient in practice. In a quiet patient lying in a horizontal lateral position, the fluid flows from a normal sized lumbar puncture needle at the rate of about one drop per second. This is usually sufficient indication of pressure.

Normal fluid is crystal clear, colourless, does not produce a clot or deposit on standing, and is sterile. Cells may be absent and are not more than five, usually mainly lymphocytes with a few endothelial cells.
The protein content varies, depending upon whether the fluid is taken from the ventricles, cisterna magna or lumbar theca. Merritt and Fremont Smith (1934) give the following figures:

- Ventricular Fluid 5 - 15 mgms. per 100 c.c.
- Cisternal Fluid 10 - 25 mgms. per 100 c.c.
- Lumbar Fluid 15 - 45 mgms. per 100 c.c.

The explanation given for the increase is that the fluid picks up the products of tissue breakdown while passing over the tissue surfaces.

The chloride and glucose content varies in normal persons roughly as the blood content varies, but Merritt and Fremont Smith's figures for normal fasting persons with normal blood values are:

- Glucose 50 - 80 mgms. per 100 c.c.
- Chlorides 710 - 745 mgms. per 100 c.c.

Given these anatomical and physiological data it is possible to appreciate the possible and probable means of spread of infection to the leptomeninges.

In the first place it is obvious that the subarachnoid space is on the whole remarkably well protected from infection by tissue planes. The dura mater forms a formidable physical barrier to infection, but there are a few weak spots in the armour. Infection can theoretically reach the
leptomeninges in the following ways:

1. By bloodstream to the meningeal vessels themselves or through the choroid plexuses in the course of a general bacteraemia, septicaemia or pyaemia.

2. By extension along the nasal lymph spaces. Obviously the most dangerous route, being the shortest, is along the olfactory filaments.

3. By direct extension from a cerebral abscess, which will itself probably have originated from a blood spread infection or as in 4.

4. By breach of the dural barrier. This in its turn can happen in various ways.

   (a) Through a congenital defect such as spina bifida or meningocele.

   (b) by damage to the dura accompanying injury such as fractured skull or open gunshot wound.

   (c) by accidental introduction of organisms during lumbar puncture or similar procedure or accidental damage to the dura during ear or nose operations.

   (d) by direct extension of an adjacent suppurative process especially if the pus is under pressure. This particularly applies to the para-nasal air sinuses, the mastoid and possibly to
infections in the orbit. In this type the advance of infection unless rapid, may be localised by the formation of adhesions ahead of the infective front.

(e) by indirect extension from a more distant infection by way of a septic thrombo-phlebitis along one of the emissary veins or other venous connections described.

(f) by a combination of two or more of these methods e.g. extension by venous route to the cavernous sinus followed by direct extension through the dura.

From the nature of the present series the proportion of primary cases is bound to be higher than normal since a case of meningitis secondary to obvious injury or primary pyogenic lesion in ear, nose or throat or elsewhere would in normal circumstances not be sent to an Isolation Hospital. However, the series gives a few cases where the evidence is strong, and quite a number of cases where the primary focus can be presumed although not proved.

It is not proposed to analyse the literature regarding primary foci, but one or two points may be made.

Straker, Hill and Lovell's nasal carrier figures, quoted previously are somewhat suggestive, and if it is accepted that infection may pass along the
olfactory filaments the seasonal incidence would in part be explained.

Applebaum and Nelson (1945) cite a series of 67 cases of pneumococcal meningitis in which 31 were secondary to ear, nose and throat conditions, two to head injury, 16 to pneumonia, while the remainder were of unknown aetiology.

White, Murphy, Lockwood and Flippen give details of another series of 71 cases of pyogenic coccal meningitis. The primary focus in 50 pneumococcal cases was middle-ear, or mastoid, in 23 cases, para-nasal sinuses in 6, Pneumonia 9 of whom 5 had positive blood cultures. Blood culture was done in 41 of the 50 cases. 23 of the 41 had bacteraemia. In the given streptococcal cases the primary foci were - diabetic foot infection with bacteraemia and endocarditis, cellulitis of eye and osteomyelitis of orbit, otitis media, and infected cerebellar scar. This small group covers several of the modes of infection described above. Four staphylococcal aureus cases had the following primary foci - 2 craniotomies, one osteomyelitis of second lumbar vertebra. The fourth case, who had had a septic abortion three months prior to admission, had a bacteraemia on admission. The meningitis was apparently cured but the patient died some months later with a subdural abscess.
In the series published by Sweet, Dumoff, Stanley, Dowling and Leppar (1945), 19 of 56 cases of pneumococcal meningitis had had pneumonia, and six had had otitis media or mastoiditis.

Honor Smith (1941) speaking of the Oxford Neurosurgical Unit showed that of 37 cases the source was otitis in 21 cases, sinusitis in 9 and fracture through a sinus in 7.

Symptoms and Signs.

All authorities are agreed that there is a close similarity in the signs of all types of meningitis and that only in minor details do differences arise.

The mechanism of production of the different signs and symptoms throws considerable light on the reasons for their appearance or absence in any particular case.

As is self evident, the essential pathological change in pyogenic meningitis as defined in the introductory paragraphs of this paper, is an inflammation of the lepto-meninges in part or in whole, caused by the presence of an organism of the order Eubacteriales (Society of American Bacteriologists classification) excluding neisseria intracellularis (meningococcus) and mycobacterium tuberculosis (bacillus tuberculosis).

On consideration it will be realised that because of the intimate contact between pia mater and the brain substance, the extension of the
subarachnoid space into the crevices of the brain substance (including the points of entry of the finest bloodvessels), and the free diffusion of cerebrospinal fluid in the subarachnoid and ventricular spaces, it is inevitable that there should be some reaction in the superficial layers of the cerebral tissues. It is in truth, to this reaction that some of the signs found in cases of meningitis are due. Thus lepto-meningitis is normally associated with some degree of aseptic encephalitis, myelitis or radiculitis depending on the severity of the inflammatory process. It is submitted that only in this way can the changes in reflexes be explained.

One of the earliest results of meningeal irritation from whatever cause it may arise, is an increase in intracranial tension. From basis principles it is obvious that there are four possible causes for this, namely increased production of cerebrospinal fluid; increased volume of blood in the cranial cavity; inflammatory exudation from damaged capillaries into the meninges and brain and into the cerebrospinal fluid; and interference with the normal reabsorption of the cerebrospinal fluid; Clinical evidence suggests that in all probability all four causes play their part, but discussion on this point may properly be postponed until the changes in the cerebrospinal fluid are considered.
The fact remains that pressure within the cerebrospinal cavity increases, and the structures within become bathed in infected fluid.

Apart from the symptoms and signs of any pre-existing disease such as otitis media, or pneumonia, and the manifestations common to any acute infection, the predominant early sign of meningeal involvement is headache. The headache may be frontal, occipital or general, and the patient may complain that he feels as if his head would burst open. That the headache is in part due to the increased intracranial pressure is demonstrated by the relief which many patients experience when cerebrospinal fluid is drawn off. That this is not the sole cause is equally shown by the fact that even reduction of the CSF pressure to normal does not usually remove the headache entirely. The character of the headache is similar in some ways to that found in the acute so-called uraemia of acute nephritis with oedema, and it appears that cerebral oedema may play a part in its causation.

The projectile vomiting so common in early meningitis is due to central stimulation by increased intracranial pressure, of the vomiting centre, which lies close to the vagal nucleus.

Bulging of the fontanelle is of course another expression of increased intracranial pressure.

In regard to some of the signs more confined to
malaria, O'Connell (1946) discusses the causation and cites experiments on the cadaver to support his hypothesis. He also discusses the opinions of other authorities on the subject.

There is a group of signs associated with increased muscle tonus and spasm in various parts of the body. These signs are neck rigidity, head retraction, opisthotonos, Kernigs sign and Brudzinski's head and leg signs. The common explanation of the signs are that they are reflex spasms designed to prevent flexion of the spine, with its attendant increase in intracranial pressure, which causes irritation of the inflamed meninges.

O'Connell maintains that the cause of the irritation of the inflamed meninges is not primarily the increase in intracranial pressure but the drag on nerve roots. He notes that the growth of the spinal medulla (and to a much lesser extent, the dura) lags behind the growth of the vertebral column and goes on to state: "From the embryological viewpoint one thus gains the impression that a state of mild longitudinal tension will persist in the intra-spinal structures - the spinal medulla, its attached nerve roots and the dural theca."

Pursuing this, he made observations on fresh cadavers after wide laminectomy opening the greater part of the spinal cord, and measured the movements of theca and medulla following various movements. On average, when the head was moved from full flexion to full extension there was a movement of the cord in relation to the vertebrae of five mm's in the cervical region and...
four mm's in the middorsal region, while the conus moved one mm. There was an accompanying observed increase in tension in the intra- and extradural roots throughout the spinal cord. With the spine allowed to flex, flexion of the hip with with extended knee produced a movement of eight to ten mm's in the cord, and tension in the roots of the sciatic nerve. Hyperextension of the hip with flexed knee produced a similar effect on the femoral nerve roots. The position of maximum relaxation of the intraspinal portion of the nerves was an intermediate degree of flexion of hips and adduction and internal rotation of the humerus. This is as found in opisthotonos. His hypothesis, therefore is that the nerve roots passing through the inflamed meninges are themselves inflamed and hyper-sensitive to mechanical stimulation. Intraspinal roots are protected from some forms of stimulation but not from the stretching produced by certain movements. He considers that the majority of signs of meningitis depend on this and are due to reflex hypertonia designed to protect the roots from tension. He explains the relative mildness of some of the signs in infants by claiming that the structures are more lax and more mobile.

The various signs are thus explained as follows: Neck rigidity. Spasm prevents the head coming forward and stretching the cord, and also prevents rotational movements which would stretch the cervical roots on the side from which the chin is turned.
Head retraction is an extension of neck rigidity and places the head in the position of maximum relaxation of the cord.

In Kernig's sign as carried out at present, when an attempt is made to straighten the knee with the hip at right-angled flexion, spasm of the hamstrings prevents the stretching described above. When Kernig's sign is strongly positive, head retraction may become more marked to relax the tension further.

Brudzinski's head sign, in which the hips and knees semiflex when the head is bent forward is virtually the last sign in reverse, as the increased tension in the neck is partially compensated for by the relaxation produced in the lumbar region.

Brudzinski's leg sign, otherwise known as the Identical Contralateral sign, (in which there is semiflexion of the free hip and knee when extension of the other knee on the flexed hip is attempted) is another reflex attempt at slackening the tension produced by the test manoeuvre.

Opisthotonos is the position in which the roots are in minimum tension and is the extreme example of protective spasm.

This hypothesis is a very attractive one and appears to hold good in various circumstances where the increased pressure theory fails. For instance, I have personally noted the presence of neck rigidity and head retraction in several cases of severe dehydration.
following gastro-enteritis in infants, where there is obviously no increased intracranial pressure as the fontanelle is depressed, and meningitis was excluded by lumbar puncture. Furthermore, reduction of the pressure in meningitis by lumbar puncture rarely abolishes the signs.

Irritation and oedema of the cortex caused by the overlying inflammatory fluid, are thought to be responsible for the convulsions in infants and the twitchings and occasional epileptiform fits in both children and adults. The general hyperaesthesia, photophobia and irritability appear to be due to a similar condition throughout the brain and cord, while the drowsiness and coma are presumably due to increased intracranial pressure and cerebral oedema. The nerve pathways close to surfaces bathed in infected CSF and underlying the inflamed meninges may be irritated or physiologically interrupted, the latter being preceded by the former. This accounts for the majority of the remaining signs, and explains why the signs may alter during the course of the disease.

The variations in the tendon reflexes depends on the location of the interruption. Diminution implies partial interruption of the primary reflex arc, probably at the nerve roots. Exaggeration of the deep reflexes are possibly due to a similar effect on the pyramidal tracts where these lie near the surface, probably at the decussation of the pyramids.
Points in Diagnosis.

From the summaries of the clinical features of the cases in the series analysed in this paper, and from cases reported in the literature, a "typical" case of meningitis may be built up. There is little difficulty in arriving at a tentative diagnosis of meningitis in a patient who complains of fairly sudden onset of severe headache of a bursting character accompanied by pyrexia, malaise and vomiting, and followed by onset of drowsiness, irritability, hyperaesthesia and later semi-consciousness, these symptoms being followed by the development of neck rigidity, head retraction and positive Kernig's or Brudzinski's sign, absent abdominal reflexes and increased knee jerks, urinary retention and constipation, and possibly sluggish pupils and photophobia.

Unfortunately, it may be said with truth that excepting the cerebrospinal fluid findings, more of the signs of meningitis is pathognomonic, nor does the absence of any sign exclude meningitis. The latter point is much the more important of the two, and is the most valuable lesson to be gained from the analysis of the symptoms and signs. The absence of the typical signs is more common in infants and young children, in whose case one is under the additional disadvantage that the patient is unable to describe symptoms. This point is seen particularly well in two of the cases seen at Rush Green Hospital (Cases 99 and 103). Neither of these children showed the typical signs of meningitis and it was mainly the unexplained ill condition of the child
and the fact that the writer was at the time "meningitis minded" that led to the diagnosis being made when it was.

The only certain method of diagnosing meningitis is by withdrawing and examining some of the cerebrospinal fluid. As this is a procedure not without risks and one which normally involves admission to hospital, there is naturally a reluctance to do a lumbar puncture where it is not essential. It is however, the writer's opinion that the risk involved in performing a lumbar puncture is far outweighed by the risk of delaying the diagnosis.

It is therefore important that the possibility of pyogenic meningitis should be kept well to the forefront of one's mind in the following circumstances:

1. When the typical symptoms and signs are presented.
2. Where the patient's condition deteriorates suddenly in the course of, or after partial recovery from an acute infection of the ear, nose or paranasal sinuses, or from pneumonia, particularly where headache is complained of.
3. Where there is a history of recent head injury even if the injury appeared at the time to be trivial.
4. In the case of septicaemia.
5. Where in the course of any infection, the patient's condition deteriorates more than one would expect from the extent of the apparent lesion.
6. In young children and infants where there is any unexplained severe illness.

In the case of the last paragraph one particular
point may be made. Gastro-enteritis in an infant may be associated with unsuspected otitis media, which is one of the commoner precursors of pyogenic meningitis. The ear drum in the very young infant may be extremely difficult to see because of the minute dimensions of the external meatus, and even if the drum can be seen there may be little or no sign of acute inflammation. One has seen several such cases personally at autopsy.

It has been my practice in recent months to treat unresponsive cases of non-specific gastro-enteritis empirically with penicillin to deal with this possibility. Such a course, although normally to be deprecated, is in my opinion justifiable in the circumstances.

Sweet (1947) goes the length of recommending that particularly in extreme youth and old age, lumbar puncture should be performed in any case where there is illness without cause and in all cases of coma, disorientation or delirium in which another diagnosis is not obvious. This injunction is possibly slightly exaggerated in regard to the older children and young adults but is well worth bearing in mind in the case of infants and old people.

Differential Diagnosis.

The differential diagnosis between meningitis and other diseases will not be considered in detail. The main diseases will not be considered in detail. The main diseases which may cause confusion are as follows:

Cerebral vascular accidents, including cerebral
haemorrhage, cerebral thrombosis and particularly sub-arachnoid haemorrhage. The onset is usually but not invariably more sudden in these cases.

**Meningism**, that is a sterile cerebrospinal fluid reaction to inflammation in adjacent structures (e.g. in mastoiditis) or to certain forms of toxaemia, particularly the virus diseases including influenza.

**Brain Abscess** either by producing pressure signs or meningism.

**Brain Tumour** especially haemorrhage into the tumour.

**Poliomyelitis** and **Poliencephalitis** before the onset of paresis.

**Glandular Fever** in some cases.

**Cervical Adenitis**, Fibrositis and other local inflammatory conditions in the spinal region producing neck or back rigidity.

**Empyema of the paranasal sinuses**.

Rare conditions such as cerebral Malaria, Encephalitis of various types, Smallpox, Typhoid, Typhus, Poisoning (lead, strychnine) Acute Alcoholism, Uraemia, Eclampsia.

The differential diagnosis between the types of meningitis is much more difficult, but is less important since lumbar puncture will usually give the required information if the possibility of pyogenic meningitis is borne in mind.

**Tuberculous Meningitis** and **Syphilitic Meningitis** are much slower in development than the average other types, but some cases of pyogenic meningitis develop slowly and closely resemble tuberculous meningitis.
Meningococcal Meningitis is more commonly primary or preceded by a recent mild catarrhal infection in the upper respiratory tract. There may be a history of living in overcrowded conditions. In the more severe and fulminating cases the typical rash may be present. In spite of these general tendencies meningococcal meningitis cannot with any certainty be diagnosed to the exclusion of the other acute forms even in the presence of an epidemic, except by lumbar puncture.

Pneumococcal Meningitis may be suspected when there is a preceding pneumonia, or of course any other known pneumococcal lesion such as pneumococcal otitis media, sinusitis or empyema especially in children in the first decade of life. A previous history of head injury appears to be rather more common in this type. The onset tends to be much more rapid than the other pyogenic types. This is shown best by comparing the average time of admission of the cases (Appendix 10-) when it will be seen that the average pneumococcal was admitted on the second or third day of disease, compared with fifth day in influenza and seventh in streptococcal. Confirming this, suspicions of meningitis was aroused sufficiently for the first lumbar puncture to be done on the third day in pneumococcal meningitis compared with forth or fifth day in influenza meningitis and seventh day in streptococcal meningitis.

Herpes appears to be more common in pneumococcal
and meningococcal meningitis than in the others. The remaining signs give little or no assistance in differentiating pneumococcal from other forms of meningitis.

**Influenzal Meningitis** should be borne particularly in mind when the patient is between the ages of three months and three years, for, as is seen in the present series, this period covers 72% of the cases due to *influenzae* but only 25% of cases due to pneumococci and streptococci. (Everley Jones (1937) describes six cases all of which were under three years of age).

68% of the cases cited by North, Wilson and Anderson (1946) were under two years of age; all the 29 children in the series described by Turner (1945) were under three years old; while Nicholson (1944) describes a series of cases with an average age of 18 months.

A higher proportion of cases of influenzal meningitis are primary (approximately 70% of the total). Hayes (1940) confirms this. Zinnemann (1946) describes a series of twenty cases of which twelve were primary. Everley Jones (1937) states that five of his six cases were primary.

The commonest primary focus in this and other series were respiratory infection, usually pneumonia (Zinnemann, 1946; Everley Jones, 1937).

The difficulties inherent in diagnosis of meningitis were naturally well in evidence especially in the Rush Green Hospital cases.
The cases of streptococcal meningitis form a more miscellaneous collection than the others. The age distribution was wide and showed no particular grouping.

The number of cases in which no primary focus is described was small (25%). Four of the nine Edinburgh cases in which there was a primary focus had ear nose or throat infections. The onset appears to have been rather slower on the whole and lumbar puncture was on average not due until the seventh day of disease.

Once more the other clinical features gave little assistance in the differential diagnosis.
CEREBROSPINAL FLUID FINDINGS

From the preceding paragraphs it is clear that the final step necessary to clarify the diagnosis is the withdrawal and examination of cerebrospinal fluid.

This is normally done by lumbar puncture, a needle being passed into the spinal theca below the end of the cord itself.

The diagnosis of all forms of meningitis depends finally on the finding of organisms in the cerebrospinal fluid. As there are several ways in which the fluid can become artificially contaminated it is perhaps advisable to consider this matter in some detail. During the period after the introduction of serum was discontinued there was less risk of introducing organisms into the spinal theca since the outflowing cerebrospinal fluid washed out any contaminating organisms. The return to intrathecal injections has renewed the danger and it is most important to take adequate precautions to prevent accidental contamination.
The essentials of the operation are as follows:
After cleaning and possibly anaesthetising the skin at the point of entry, a stiletted needle is introduced into the theesa in the third, fourth or fifth lumbar space. Fluid is allowed to flow into a container which has a stopper. Fluid to be injected is drawn up in a syringe and injected.

Analysing this procedure it can be seen that there are many possible sources of contamination, even if commonly used methods are adhered to.

The matter is considered in detail in the Medical Research Council's memorandum on the Sterilisation, Use and Care of Syringes (1945) and the more recent memorandum from the Public Health Laboratory Service and the London Sector Pathologists' Committee (1947) published in several journals.

Briefly the possible sources of contamination are as follows:

1. Inadequate cleaning of instruments before sterilisation.
2. Inadequate sterilisation of instruments e.g. attempted chemical sterilisation.
3. Contamination of instruments in 'laying up the
trolley' by
(a) use of contaminated needles.
(b) cooling syringes by pouring 'sterile' cold water over it.
(c) serving instruments in spirit.
(d) leaving the instruments exposed to airborne infection for some time before the L.P.

4. Inadequate washing of operator's hands including use of unsterilised nail brushes. (Sebrechts: 1947)

5. Inadequate sterilisation of the patient's skin.

6. Contamination of the operator's hands while finding landmarks, etc., and cleaning up skin.

7. Use of nonsterile local anaesthetic or contamination of the hypodermic needle etc. during withdrawal from an open or rubber-capped phial.

8. Carrying in of infected tissue from the deeper layers of skin. This may occur if a needle without a stilette is used.

9. Injection of contaminated solutions due to
(a) use of an inadequately sterilised syringe.
(b) contamination of the solution during preparation.
(c) Contamination of the solution caused by taking several doses from the same container.

10. The fluid withdrawn may be contaminated
(a) in any of the ways mentioned above.
(b) if accepted into an unsterile container.
(c) if the mouth of the container is touched by the attendant nurse.
(d) if the plug or cap is contaminated by the nurse.

Apart from paragraph 10 which confuses the laboratory examination, the commonest fault is probably the use
of so called sterile water which has been contaminated. A common organism in such cases is pseudomonas pyocyanea.

Barrie (1941) reported eleven cases of meningitis traced to a defective Berkefeld filter which had ill advisedly been considered as producing sterile water. Smith W. and Smith M.M. (1941) investigated eleven samples of "sterile" water from hospital wards and found six of them contaminated. In 223 unselected specimens of cerebrospinal fluid nonpathogenic contaminants were found in 89. 37% of these organisms were waterborne. Frankis Evans (1945) also reports contamination of "sterile" water from a Winchester.

As an example of contamination of fluid for intrathecal injection one may quote the investigation made by Harris, Buxbaum and Applebaum (1946). They found that although the technique appeared to be faultless in other respects, the penicillin was taken from the same phial both for intrathecal and intramuscular injections, and although the syringes used for intramuscular injection had been adequately sterilised, they were stored in a jar contaminated with
ps. pyocyanea.

After various alterations of technique during the poliomyelitis outbreak of 1947 the following procedure has been evolved as a reasonable compromise between theoretical perfection and practicability, taking into consideration shortage of rubber gloves and syringes and shortage of trained nursing assistance.

The syringe for local anaesthesia and the needles are placed in a kidney dish and boiled up for at least five minutes, after which the water is tipped from the dish but the contents are not touched with the bowl forceps. The dish and contents are transferred to a trolley laid up with sterile towels and gallipots. Two one ounce screwcap bottles, previously sterilised in the hot air oven, are included in the sterile packets for lumbar punctures. The trolley is covered with a sterile towel and used almost immediately.

The patient is placed in position and the site for injection provisionally identified by palpation. This avoids excessive handling later.

The operator and assisting nurse should wear
masks. The operator scrubs up and dries his hands on a sterile towel, and cleans with ether and iodine an area of skin larger than the hole in a serum towel which is now draped over the area. (A towel with a six inch circular hole gives good access and does not fall off so readily if the patient moves)

Local anaesthetic from a 1 c.c. glass ampoule is injected. (A general anaesthetic is occasionally required in very restless patients.) The needle is introduced in the usual way, taking care not to touch the tip and to avoid as far as possible touching the shaft. The stilette when removed is laid only on a sterile towel. The C.S.F. is allowed to run into the screwcapped bottles which, being sterile outside as well as inside, can be handled by the operator. Having tested for block by Queckenstedt's method enough C.S.F. can be removed to bring the pressure to normal.

The syringes for intrathecal injection are all-glass syringes sterilised in the hot air oven. The solution for injection should be made up in single dose ampoules. For 5 c.c. doses or less screwcapped bijou bottles may be used. Alternatively rubber capped phials may be used such as are illustrated in the M.R.C. War Memorandum on the Sterilisation, Use and Care of Syringes (1945) (a rubber capped bottle with an outer protecting bakelite cap incorporating an absorbent pad
impregnated with chloroxygenil). After withdrawing about an equivalent volume of C.S.F. the solution is injected.

A gauze pad impregnated with collodion is placed on the puncture wound.

One of the samples of C.S.F. is intended for immediate examination, cell count and inoculation of media, and later chemical estimations, while the other is incubated as it is at 37°C.

An immediate examination ensures an accurate cell count and gives no time for any possible contaminant to grow.

A direct film stained methylene blue gives a better picture of cellular and bacterial morphology than a Gram film and can be examined while the Gram film is staining.

The important point at this stage is to be sure before reporting "Gram negative diplococci morphologically resembling meningococci", particularly if the organisms are scanty. Some of the coccobacillary forms of h.influenzae appear to be diplococcal, and degenerate cocci, especially pneumococci, may lose their Gram positive staining properties and appear as Gram negative cocci.

It is much more satisfactory if laboratory facilities and staffing permit culturing of all
organisms found in C.S.F. Pneumococci and streptococci and meningococci will grow in C.S.F. but are best cultured on a blood agar plate as pneumococci and strep.viridans are in some ways similar, and haemolytic streptococci can be detected. Incoculation of a heated blood agar plate gives the best chance of growing any h.influenzae, especially if seeded with staphyloccoci to demonstrate "satellitism" (i.e. more rapid growth in proximating to the staphylocccodal colonies due to the production of 'V' factor by the staphyloccocus).

The media should contain para-amino benzoic acid or penicillinase respectively if sulphonamides or penicillin have been administered prior to lumbar puncture.

Blattner, Heys and Hartmann (1943) report that growth can be obtained in egg cultures both earlier and later than in the usual blood agar plates. This form of culture is of course too complicated for use except in a few large centres but demonstrated that absence of growth on blood agar does not prove sterility of the fluid.

It will have been seen that the cerebrospinal fluid in pyogenic and meningococcal meningitis is almost invariably cloudy, and contains a large number of cells, predominantly polymorphs. In a few cases the relative lymphocyte count may be high. It must
on the other hand be borne in mind that in poliomyelitis and tuberculous meningitis, where the C.S.F. is usually predominantly lymphocytic, polymorphs may predominate at the outset of the disease. Also cerebral abscess near the meninges may produce a sterile fluid with increased polymorphs.

The sugar is usually absent or considerably diminished but this may not be obvious very early in the disease. The fall is presumed to be due to the organisms breaking it down.

Chlorides are usually lowered although not to the same extent as may be found in tuberculous meningitis. Part at least of this fall is due to the lowering of the blood chlorides caused by the vomiting which is an early feature of the disease.

It will be seen from Appendix 10 that the average figure for C.S.F. chlorides on first lumbar puncture was 649 mgm per 100 c.c. in pneumococcal meningitis, 690 in influenzal, and 606 in the single case in which a figure is given for streptococcal meningitis. This does not agree with Hayes (1940) who asserts that the lowest chloride values (other than in tuberculous meningitis) are found in influenzal meningitis. He also states that the prognosis is worse in cases in which the chlorides are low. The figures in the present series are too small to confirm
or refute this statement, but one of the cases of influenzal meningitis had a C.S.F. chloride value of 554 mgm per 100 c.c. at one point.

C.S.F. protein is increased to a variable extent. In the present series the value varied between 45 and 1500 mgm per 100 c.c. C.S.F. The latter figure was obtained in a case of streptococcal meningitis. The average C.S.F. from pneumococcal meningitis had a considerably higher protein content than that from influenzal meningitis but it is doubtful if this is significant in view of the size of the series.

The finding of the organisms is, of course, the clinching diagnostic point, provided that no contamination of the fluid has taken place since withdrawal.

In pneumococcal meningitis as has been seen the organism may be scanty, but may, on the other hand, be overwhelmingly copious so that the fluid has a frosted glass appearance.

The serological type has been determined in many cases but the results show a wide diversity of types of infecting organisms. Twenty-three cases of the Edinburgh series fall into fourteen types. Applebaum and Nelson (1945) record a series of 67 cases which fall into twenty serological types, while Joppich (1933) records a series of 28 cases with thirteen types.
involved. Type 3 is the commonest of all the types and is also found frequently in otitis media.

In the case of influenzal meningitis, however, the vast majority are due to one serological type. The investigations which led to this discovery are associated with the name of Margaret Pittman, who, in 1931, published the results of an investigation on various strains of haemophilus influenza. Of 97 strains showing the general characteristics of h. influenzae she found that 15 produced an unusual type of colouring on Leventhal's medium. These were relatively large - up to 3mm in diameter, slightly opaque with a smooth surface and slightly mucoid appearance, with iridescence in oblique light. A film from the colonies at this stage shows short uniform rods showing capsulation. The capsules produce a soluble carbohydrate specific substance which can be demonstrated on filtrates or washings from cultures. Antigenically she divided these at the time into two types, a and b. These typical appearances are seen to advantage only on Leventhal's medium, and even on this older cultures revert from the S form described above to the R variant which has the appearance of typical h. influenzae in films and culture. This change occurs in about 48hrs. Wright and Ward (1932) confirmed Pittman's observations on this point and
showed that the rough variants were more susceptible to the bactericidal action of blood. Filtrates from smooth cultures inhibited the bactericidal action of blood on smooth forms while filtrate of rough cultures had no such action. Seven of the fifteen strains described in Pittman's (1931) paper were isolated in pure culture from the C.S.F. in cases of influenzal meningitis. All of these were type b. Since Pittman's original work the smooth form has been subdivided into six types (a to f) instead of two. Type b is the commonest and Pittman (1933) found that with few exceptions influenzal meningitis was due to this type. Straker (1945) has typed 23 strains of smooth h. influenzae since 1942. Of these, 21 belonged to type b. Zinnemann (1946) reports on 20 cases of influenzal meningitis of which 19 were caused by Pittman's type b. Straker also states that throat swabs mostly show R. types but up to 8% contain S types. The fact that the S type causes meningitis, may be linked up with the production, presumably by the capsules, of the substance which inhibits the bacteriostatic properties of the blood as described by Wright and Ward.

The cases of streptococcal meningitis were due to several types including haemolytic streptococci, streptococcus viridans, and a number of cases where the type was not ascertained the figures are too small to
draw conclusions from.

A point of caution must be mentioned. Contamination of cerebrospinal fluid by organisms can, of course, give rise to the erroneous diagnosis of the type of meningitis. Where there is doubt a blood culture may be of assistance as a proportion of cases have a demonstrable bacteremia, especially in the early stages. Applebaum and Nelson (1945) report 33 cases with positive blood culture and 16 with negative blood cultures in a series of cases of pneumococcal meningitis. Boisvert, Fousek and Grossman (1944) and Hayes W. both report successful isolation of H. influenzae on blood cultures, while cases of meningitis due to streptococci and salmonella Dublin in the present series both had positive blood cultures.
TREATMENT

Presulphonamide Period

The mortality rates prior to the advent of the sulphonamides were extremely high in all forms of non meningococcal meningitis, and even the recovery figures collected from the literature by various writers are certain to be higher than the genuine rates, as fatalities, which are not news, are less frequently published than recoveries, which are news.

Wyllie (1940) quotes two investigations of the literature, one carried out by Goldstein and Goldstein (Internat. Clin. 1927;3:153) and the other, following up the first, by Hewell and Mitchell (J.Amer. Med. Ass. 112:1033). These authors in a search of the literature found only 180 recoveries from pneumococcal meningitis before 1937. Waring and Smith (1944) give the presulphonamide mortality rate in pneumococcal meningitis, in Baltimore, as 100%.

Influenzal meningitis bore a mortality of between 92% and 100% in the same era. Beck and Janney (1947) report that 63 out of 65 cases of influenzal meningitis died in the period 1923-39. North, Wilson and Anderson quote various series in all of which the overall mortality was over 96%.

Streptococcal meningitis was about 97% fatal.
(Wyllie, 1940), and the same writer quotes Michels and Gonne (Am. J. Dis. Child 1939:67:1379) as having found only eight recoveries in staphylococcal meningitis up to 1938.

The treatment in those days depended on general measures which were mainly palliative, operative procedures mainly designed to deal with the primary focus, and specific serum therapy.

**Non-Specific Treatment**

This is perhaps the best point at which to discuss non-specific treatment, as it is applicable throughout the three periods. Removal of primary focus is obviously indicated when possible as there is a risk of reinfection of the meninges from a persistent primary focus even if the meningitis has been controlled. In the case of collections of pus in close proximity to the meninges it has been argued that operative procedures may disturb the leucocyte barrier and precipitate a worse state than before. This will be referred to again in the section on the Penicillin period. There is of course the tendency to consider that the operation risk is too great, but this must be set aside as there is little hope of recovery in any case where the primary focus remains.

Direct drainage of the meninges is a procedure which may be successful in meningitis secondary to
labyrinthine disease (Jenkins, 1922). In these cases there may be at least partial localisation of the meningitis. He also recommended combining trans-labyrinthine drainage with lavage from a lumbar puncture, using a modified saline solution, but the value of such procedure is doubtful. Repeated lumbar punctures do at least give temporary, if partial, relief and on the general principle of removing infected material this form of treatment appeared to be rational and was employed in the pre-sulphonamide period. If the absence of block is demonstrated by Queckenstedt's test, and the fluid runs out freely, there does not appear to be any reason why a relatively large amount of fluid should not be removed. On the other hand, of course, the first sign of spinal block (such as a rapid clearance of pressure or rate of flow) is the signal to stop withdrawing fluid. The above remarks apply where the meningitis is definite. Where there is any possibility that there may be a cerebral abscess or tumour present, only a few millilitres of fluid should be removed because of the risk of block and/or bursting of, or bleeding into, an abscess close to the subarachnoid space. The situation altered after the introduction of sulphonamides and antibiotics, owing to the necessity of building up a concentration of the drug in the
cerebrospinal fluid. Repeated punctures for the purpose of drainage have now been given up.

The development of block is an incident which renders treatment difficult in various ways and leads to hydrocephalus if not overcome. Various manoeuvres have been used to attempt to dispose of blocks. Shalom (1945) considers that many cases of spinal block are due to the cerebellum and medulla being pushed back by intracranial pressure to cork the foramen magnum. He describes a case of longstanding pneumococcal meningitis where a spinal block appeared with low C.S.F pressure and clear fluid in the lumbar region but high intraventricular pressure. The left ventricle contained pneumococci. Patency between the two lateral ventricles was demonstrated when air introduced into the left ventricle was recovered from the right. Release of intraventricular pressure undid the blocks and turbid fluid appeared in the left ventricle and lumbar theca. Two days later the block had reformed and the patient was unconscious. Hypertonic solution was given intravenously, the lumbar puncture needle being left in site with the manometer attached. In less than ten minutes, just before the patient recovered consciousness, the fluid in the manometer rose to about 200 mm and then fell to 80 mm. Queckenstedt's test again became positive. The
explanation appears to be that the hypertonic solution raised the osmotic tension of the blood, thus causing C.S.F. to be reabsorbed into the choroid plexuses, and tissue fluids to be reabsorbed into the blood in the cerebral capillaries. The resultant shrinking of the brain and reduction of intracranial pressure releases the pressure on the medulla, and as it were "uncorks" the foramen magnum. This appears to be a useful manoeuvre if the block is detected early.

Shalom's paper was criticised on some points by Jepson and Whitty (1945) but Shalom replied with a report of a further five cases in which the procedure was successful without intraventricular puncture. The hypertonic solution used in the later cases was 50% dextrose up to 50 c.c. 2hrly. for twenty-four hours.

Alexander (1944) has used air and heparin intrathecally to clear blocks.

Failing successful clearing of the block by such methods it is necessary to perform a cisternal puncture (which may be a matter of some danger if the medulla is pushed down into the foramen magnum) or intraventricular puncture, either through the fontanelle in infants or through burr holes in adult patients.

Other Non-specific Treatment Symptomatic treatment such as the use of sedatives including morphia where
necessary is, of course, required. Particular attention must be paid to relieving retention of urine which can cause great restlessness and delirium in the semiconscious patient.

**Serum Treatment**

Pneumococcal type specific serum has been used but the mortality figures quoted above show that little success has been achieved. The patient has probably passed beyond help before the organism has been cultured and typed and the appropriate serum obtained. Polyvalent sera are of little use because so many types are involved in the causation of meningitis as is seen in the present series and those quoted above. Influenzal meningitis is in a different situation as the vast majority of cases are caused by haemophilus influenzae of Pittman's type b. Pittman (1933), Ward and Wright (1932) and others produced horse antisera by injecting horses with h. influenzae isolated from cases of meningitis. Finding that complement was absent from the C.S.F. in influenza meningitis, they added fresh human serum before injecting the serum intrathecally. The results were disappointing and although there was temporary improvement, most cases died. According to Zinnemann (1946) the mortality rate was reduced from 97% to 80-84%. Zinnemann, in the paper quoted, gives a
concise summary of the further progress in this field and quotes the results obtained by Alexander and others following her production of anti-haemophilus influenzae type b rabbit serum instead of horse serum. Although its efficacy alone was proved (North, Wilson and Anderson, 1946, report 132 recoveries out of 184 cases in several series) it was soon found that the results when combined with sulphonamides were better, as will be seen later. Unfortunately no considerable amount of Alexander's serum has been produced in this country, so that figures relating to its results in patients here are not available.

Streptococcal meningitis has from time to time been successfully treated with serum alone. A fairly recent case of successful serum therapy is reported by Schwartz (1938) who treated a girl aged 7 years suffering from haemolytic streptococcal meningitis following otitis media. Two intramuscular injections of 3,000 and then 6,000 units of streptococcal antitoxin (scarlatinal type) produced no benefit, but 9,000 units intravenously for three days produced a fall in temperature. The next day a further 9,000 units intramuscularly was followed by a rise in temperature. Four further intravenous doses of 9,000 6,000 6,000 and 4,500 produced a lasting fall in temperature and general recovery. Recoveries are rare.
In the series under review no serum was employed (other than the anti-meningococcal serum which was injected before the true diagnosis was ascertained). There is no evidence to show that the use of anti-meningococcal serum has a beneficial or deleterious effect on patients not suffering from meningococcal meningitis, so treatment with this serum may be ignored.

The mortality in all types of pyogenic meningitis in the present series prior to the introduction of sulphonamides was 100%.

**Sulphonamide Period**

The introduction in 1935 of the sulphonamide dosage opened a new era in medicine, and, once sulphonamides became available it was not long before the successful treatment of some cases of meningitis began to be reported. At first the dosage and methods of administration were tentative and irregular, and to this day there is no complete agreement on the best dosage, although the Medical Research Council (1945) has produced a memorandum which gives useful guidance, including a skeleton scheme for treatment of the various types of pyogenic meningitis.
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The earliest encouraging results were obtained with streptococcal meningitis for the reason that sulphonamide is relatively ineffective against the pneumococcus and haemophilus influenzae. The three main types will, however, be considered in the same order as heretofore.

**Pneumococcal Meningitis.** One of the early recorded cases of recovery reported in this country is that reported by Caldwell and Byrne (1937), a girl of 16 years in the second day of disease. Prontosil was given by mouth and intramuscularly, and she recovered fully in nine days, after being blind for two days. Several lumbar punctures were done, and the authors are not prepared to claim that the cure was necessarily due to the prontosil. However, sporadic cases continued to be recorded. Young (1938) reports recovery in a boy of five who received 23 Gms of sulphonamide in 13 days. Neal and Applebaum (1938) report three recoveries in 14 cases. The organisms were types 4, 19 and 31.

After the introduction of sulphapyridine in May 1938 by Whitby (1938) the recoveries began to be more frequent. Reid and Dyke (1939) report the case of a girl aged 7 years who made an uninterrupted recovery following a course of sulphapyridine. Cunningham (1938) reported a recovery in a woman of 47 years who
was first treated with sulphanilamide. Following
deterioration in condition sulphapyridine was given
literally ad nauseam.

Coleman (1940) reviewing the cases to date reports
a reduction in mortality to about 35% Once more one
imagines that the figures are a little optimistic.

In the series under review the mortality rate
during the Sulphonamide period was 85%, or 63% if
those treated with Sulphapyridine are considered
separately, but the average period of survival of thefatal cases increased from 5 to 10 or 11 days from
onset.

Dowling, Dauer, Feldman and Hartman (1942) report
on a series of 72 cases in which the overall mortality
was 68 out of 72 (94.5%). They classify the cases into
four groups according to treatment. All four
recoveries were in the group of 39 who had "good"
treatment. (i.e. 4 - 6 Gms Sulphonamide followed by
10m 4 hourly in adults; no lapes in treatment until
death or recovery). The survival of the fatal cases
was 7-5 days where treatment was "good", and 2-5, 2-1,
and 1-2 when it was "fair", "poor" or "none"
respectively. They found that many organisms and few
cells in the C.S.F. was a bad prognostic sign.

Nokes, Smith and Iokes (1943) gave adults 3 Gms
of Sulphonamide intravencously, and 2-4 Gms by mouth,
followed by 1·5 Gm 4 hourly.

The dosage recommended by the Medical Research memorandum was as follows:

In the adult 2-4 Gms intravenously and 1·5 Gm by mouth followed by 1·5 Gm 4 hourly for four days, 1 Gm 4 hourly for 2 days, and 6 hourly for two days, followed by 0·5 Gm 6 hourly for at least seven days, making a total of about 82 Gms in 15 days, compared with the dosage recommended for meningococcal meningitis of about 50 Gms in 7 days.

The amounts employed in the cases treated with sulphonamides alone in the present series were more in accord with the dosage for meningococcal than for pneumococcal meningitis. In the light of later experience it would appear that with the use of higher dosage in the same time the recovery rate might have been raised. It will be recalled that the average adult dose in the recoveries was 60 Gms and that each of the cases received more than the then standard course. In a number of fatal cases the drug was stopped after the standard course had been given and restarted a few days later when relapse occurred. Later experience again suggests that the risk of toxic effects of high sulphonamide dosage should largely be ignored and that the drug should not be stopped until recovery is virtually assured, or until death. That it
is not sufficient to regard the cerebrospinal fluid as sterile when culture on the usual media fails can be understood from the work of Blattner, Heys and Hartmann (1943) who when examining C.S.F., were able to produce positive cultures in the chorionicallantoic membrane of developing eggs three days after culture on blood agar had become sterile. Treatment should therefore be continued for several days (at least four, and probably seven) after no organisms can be isolated from the C.S.F. on normal culture.

Later sulphonamides of lower toxicity have been employed, and although only a few cases in the Edinburgh series were treated with them during the "sulphonamide alone" period it is appropriate to mention them at this point.

Those employed in the series and in the Rush Green Hospital cases were Sulphathiazole, Sulphadiazine and Sulphadimethylypyrimidine, the last in the form of "Sulphamezathine". The proportion of sulphonamide which penetrates to the cerebrospinal fluid varies with the drug. Taking the concentration in plasma as 1.0, that in the cerebrospinal fluid is sulphapyridine 0.7, sulphathiazole 0.15 - 0.4, sulphadiazine 0.5 - 0.8 (Medical Research Council 1945), and the figure for sulphamezathine is thought to be low.
The last drug is rapidly absorbed from the gut and slowly excreted, is remarkably free from toxic reactions, and rarely produces crystallisation in the renal tract. These factors outweigh the lower absorption into the C.S.F. and make it a suitable drug for use in meningitis, where prolonged and heavy dosage are frequently required.

There is no great difference in the efficacy of the drugs against the pneumococcus but sulphathiazole is less commonly used now because of the relatively poor blood concentrations and poor absorption from blood to C.S.F. Sulphapyridine is somewhat irregular in its reaction so that the commonest drugs employed today in the treatment of meningitis are sulphadiazine and sulphamethazine, the former being more frequently used.

A number of reports recorded treatment with sulphonamides and type specific sera. Hodes et alia (1943) reports 13 recoveries in 29 cases treated with serum and sulphonamide, and 12 recoveries out of 31 cases treated without serum. In the patients under two years of age 6 out of 18 recovered with sulphonamide and serum and only 1 out of 14 treated without serum. The serum was given intravenously in doses of 20,000 to 40,000 units daily until the patient's serum diluted 1:5 produced capsular swelling.
in the patient's organism.

Influenza Meningitis. Cases of recovery from influenzal meningitis following treatment with sulphonamides began to appear in the literature somewhat later than pneumococcal cases. The earliest sulphonamides had little success in treating the condition although a few cases were reported (e.g. Teggart, 1938). Sulphapyridine produced a number of recoveries (e.g. Roberts, 1938; Roche and Caughey, 1939; Matthews, 1943; Moir, 1943; Birch, 1943; Archer and Singer, 1943). Sulphadiazine began to produce slightly better results. Sako, Stewart and Fleet (1942), for instance show five recoveries in seven cases treated with the drug. The maximum dosage given was 92 Gms in 26 days to a child aged 2 years.

In the Edinburgh series no recoveries were recorded except in cases treated with heavy doses of sulphadiazine (with or without other sulphonamides). Three out of the four treated with sulphadiazine lived. Taking the whole group together the mortality was 75% compared with nil previously, and the average survival of the fatalities was 31 days compared with 11 previously.

Thus once more sulphadiazine appears to be one of the drugs of choice in this form of meningitis.
Specific antiserum treatment, using Alexander's anti-haemophilus influenzae type b rabbit serum, which had been found disappointing on its own, was tried with some success in combination with sulphonamides. Almost all the work on this subject has been done overseas, namely in America and Australia. No figures are therefore available for this country.

Knouft, Mitchell and Hamilton (1942) report a series of 63 cases in four groups. The first group received symptomatic treatment only and all died. The second group received Fothergill's anti-haemophilus influenzae serum. All died, the average survival being 7.4 days. The third group of 13 had Fothergill's serum and Sulphanilamide. One girl aged six admitted on the second day recovered after 93.5 Gms of sulphanilamide (discontinued after ten days because of jaundice and anaemia) 100 c.c. anti-influenzal serum was given intravenously on admission and eight hourly until 791 c.c. had been given. After four days intrathecal serum 15 c.c. with 5 c.c. complement was given daily for 12 days. The C.S.F. became sterile in 7 days and remained so. Recovery was complete. The fatal cases survived on an average 15½ days.

The fourth group of 12 children, aged 3 months to 8 years, was treated with serum and sulphapyridine, with blood transfusions, dextrose and vitamins as
adjuvants. Sodium sulphapyridine was given by intravenous drip for three days, whether or not the patient could swallow, and this was followed by oral administration until two weeks after the C.S.F. became sterile, because of the tendency for influenzal meningitis to relapse, a contingency which was guarded against by lumbar punctures every few days. Nine patients recovered. The intravenous drip administration certainly ensured that the sulphonamide is received by the patient. It is a little difficult to judge what proportion of this success was due to intravenous administration and what was due to the change to sulphydryline.

Turner (1945) reports a recovery rate of 50% in a series of 20 cases who had full doses of Alexander's type b specific antiserum together with sulphapyridine or sulphadiazine. This compares with a mortality rate of 81.3% for the preceding six years.

North, Wilson and Anderson in a heavily documented paper gives a survey of treatment as compared with previous forms of therapy. In series of 157, 150 and 87 cases treated respectively without specific treatment, with sulphonamides, and with sulphonamides and serum, there is a progressive improvement in recovery rates from 1.2% in the first group and 22% in the second group to 56.6% in the third and last group.
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Turner (1945) reports a recovery rate of 50% in a series of 20 cases who had full doses of Alexander's type b specific antiserum together with sulphapyridine or sulphadiazine. This compares with a mortality rate of 61.3% for the preceding six years.

North, Wilson and Anderson in a heavily documented paper gives a survey of treatment as compared with previous forms of therapy. In series of 157, 150 and 87 cases treated respectively without specific treatment, with sulphonamides, and with sulphonamides and serum, there is a progressive improvement in recovery rates from 1.2% in the first group and 22% in the second group to 56.8% in the third and last group.
They explain this by postulating that sulphonamides inhibit H. influenzae but that antibody is required to give the organism its final quietus. Alexander's dosage of serum varies in inverse ratio to the amount of sugar present in the C.S.F. This she estimates by adding 1 ml. Benedict's reagent to serial dilutions of C.S.F. containing 0.05 to 0.25 ml. C.S.F. by steps of 0.5 ml. If all five tubes are reduced the sugar is considered to be over 50 mgm%. If one tube is reduced the sugar content is considered to be under 20%. The dosage is as noted in the following table.

<table>
<thead>
<tr>
<th>C.S.F. sugar (mgm %)</th>
<th>Antibody Nitrogen indicated (mgm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 15</td>
<td>Less than 150</td>
</tr>
<tr>
<td>15 - 25</td>
<td>150</td>
</tr>
<tr>
<td>25 - 40</td>
<td>75</td>
</tr>
<tr>
<td>Over 40</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>25</td>
</tr>
</tbody>
</table>

Criteria for estimation and control of dosage are given.

The average dose given to the children was 130 ml, rarely given in more than two doses. Intramuscular treatment produced better results than intravenous injection in infants under 2 years. Intrathecal injection is not recommended.
Streptococcal Meningitis

As might be expected from the response of streptococcal infections elsewhere in the body, encouraging results were obtained early in the career of sulphanilamide, and many recoveries were reported in the literature in 1937 and 1938. In a review of the early literature Tyson (1938) quotes a number of cases in which sulphanilamide in weak solution was given intrathecally, apparently without ill results. It is probable that the solutions were of the original sulphanilamide and not of the sodium salt. As later experience proves, the sodium salts of sulphonamide drugs must on no account be given intrathecally, as temporary or permanent paraplegia can result. Occasional incidents of this sort continue to be reported (e.g. Lancet 1946;2:403). The drug was given intrathecally, intramuscularly, subcutaneously and orally in different cases. The general dosage defies classification but appears to have been in the region of 6 Gms daily for several days after which small doses were given.

Early cases reported in this country are those published by Lucas (1937), Thomas (1937), Frazer (1937). Sporadic cases treated with sulphapyridine and other more recent sulphonamides continue to appear.
The effectiveness against strep. viridans is small, but recoveries have been reported.

Lowenthal (1933) experimenting on mice showed that sulphonamides and serum combined protected mice against haemolytic streptococci more effectively than either alone. This compares with the findings in meningitis due to haemophilus influenzae.

As regards the Edinburgh series it will have been noted that although there were no recoveries among the five cases the average survival period rose from 12 days to 34 days.

Penicillin Period

Penicillin was discovered by Fleming in 1928, but was not, because of lack of facilities and chemical investigation, produced in a form suitable for therapeutic purposes until 1940. After this the necessities of the fighting services accelerated research on both sides of the Atlantic, but also absorbed almost all the production of penicillin. Those at home were therefore kept very poorly supplied with this substance of which so much was expected.

The result was that various means were adopted of maintaining sufficiently high concentration in the tissues with the minimum amount of penicillin.
Various forms of apparatus for continuous administration by intramuscular drip were evolved, it having been established that intravenous injection offered no advantage over the others. The apparatus used for this purpose at Edinburgh City Hospital was the Endrip, a system of controlled air entry into an inverted six ounce bottle from which the penicillin solution dripped at the rate of 100,000 units daily, thus maintaining the body tissue concentration continuously at a level effective for the average penicillin sensitive infection in the body. The alternative method of administration was by repeated injections, usually three hourly in doses usually of 20,000 units. The discovery since that time that penicillin is bacteriostatic in the above concentrations, but is bactericidal in higher concentrations, coupled with the increased availability of the substance has led to much larger doses being employed at longer intervals (e.g. 200,000 units eight hourly by subcutaneous injection). Because of the rapid excretion of penicillin the total number of units used is of little value in comparison unless the mode of dosage is known.

An oil wax suspension was introduced to try and avoid frequent doses of small quantities by slowing absorption. The preparation was difficult to handle
and gave considerable pain and the writer has abandoned it in favour of heavy dosage of aqueous solution.

It is of interest to note that Fleming's first case in 1942 was a man suffering from streptococcal meningitis and apparently dying, who recovered after intramuscular and intrathecal administration of the whole meagre stock of penicillin in the country (Fleming 1943). This case caused penicillin to be brought to the notice of the Government and initiated its production on a large scale.

The other important change in recent years has been the increasing purity of penicillin from 1.5 units per c.c. of concentrate in the early days to approximately 1500 units per mg of "crystalline" penicillin today. This is of great importance in the treatment of meningitis because some of the impurities associated with the earlier extracts were intensely irritant when introduced intrathecally, and in some cases produced permanent damage.

Unlike sulphonamides, penicillin does not pass through the healthy meninges in effective amounts. The inflamed meninges do, on the other hand, pass a certain amount of penicillin (Rosenberg and Sylvester 1944) as can be seen from Case 51 of this series, but not enough for full therapeutic purposes.
The usual intrathecal dose is in the region of 20,000 units daily made up in 2 c.c. to 20 c.c. of saline or water. The stronger concentrations were generally frowned upon because of the irritant effect of the impurities, but the crystalline penicillin allows greater concentration. Reuling and Cramer (1947) quote a case where 500,000 units in 10 c.c. were injected intrathecally in error for 50,000 units. Convulsions resulted but the patient recovered completely.

The sensitivity of organisms to penicillin varies considerably from species to species and even among strains of the same organism, and in any case which it is proposed to treated with penicillin this sensitivity should be tested; but where facilities for this are not available there is no case for withholding the drug. The basis for most sensitivity tests is the presence of a zone of inhibition of growth of the organisms concerned round a small amount of penicillin in a cup or trough in an agar plate, or failure to grow in solutions containing various strengths of the drug. Daguid (1946) has shown that all organisms are in some degree sensitive to penicillin, but that the concentrations required to inhibit some of these (e.g., Myco.tuberculosis) is too high to be attained in vivo.

Bigger (1944) demonstrated an invitro synergistic
action of penicillin and sulphonamides on staphylococcus aureus cultures in broth. This has been confirmed in vivo in general experience.

**Pneumococcal Meningitis.**

Cairns, Lewin, Duthie and Smith (1944) published a series of sixteen cases in which they had tried various means of introducing the drug into the cerebrospinal fluid spaces. They had the disadvantage of working with impure preparations containing 50 - 100 units per milligramme. These produced a severe reaction in one case. Twelve of the cases recovered. Two of the four deaths were due to cerebral abscess, and the other two followed attempts to treat the condition by intrathecal injection only. Of the first eight cases in the series only three received parenteral penicillin other than intrathecal penicillin. One man was cured with 20,000 units only, while a man who received 85,500 into the CSF spaces and 2,770,000 units otherwise, died.

Smith records 29 fully treated cases (i.e. excluding rapid deaths) with 25 recoveries. The deaths occurred in the first 16 cases which were treated with penicillin alone. All the cases treated with penicillin and sulphonamide recovered. The routine treatment included penicillin 8,000 to 20,000 units intrathecally and 120,000 units penicillin intramuscularly in each 24 hrs. Sulphadiazine was given by mouth or nasal tube (4 Gm, then 2 Gm 4 hourly). Repeated lumbar
punctures are required to reduce risk of block. Three of the fatal cases died in relapses after cessation of treatment.

White, Murphy, Lockwood and Flippin (1945) published a series of 71 cases of Meningitis of which 50 were pneumococcal. The mortality rate was 64%. The standard dosage was 100,000 units daily to an adult. The average total dose in the recoveries was 1,400,000. The cisternal and ventricular routes were employed where necessary because of block or failure to respond to penicillin by the lumbar route. 21 cases had 10,000 units penicillin intrathecally daily. Of these 14 died whereas all four cases treated with 15,000 to 20,000 units survived. Again the figures are small, but suggestive on this point.

Of the 71 cases, 23 cases were secondary to infection in the middle ear or mastoid and 6 in the paranasal sinuses. The mortality in these 29 was 71.4% compared with 55.5% in those secondary to pneumonia and 50% in the 12 cases where no primary focus could be found. The mortality rate in those given penicillin by lumbar puncture only, was 73% while 46.7% of those who received penicillin in the cistern or ventricles died.

Applebaum and Nelson (1945) treated 67 cases with penicillin, the average case receiving 175,000 units intrathecally and 400,000 units systemically. In all but three cases, sulphonamides were stopped before penicillin treatment was started. The mortality rate was 61%.
Smith, Duthie and Cairns (1946) in reporting 38 cases treated with penicillin and sulphonamides stressed the danger of delay before instituting treatment, and recommend that sulphonamide treatment be given until the final diagnosis is made, but consider that operation on the primary focus should if possible be delayed.

Most writers emphasise the necessity for continuance of treatment beyond the time of clinical improvement.

Cairns (1947) states that high dosage of crystalline penicillin intrathecally may cause severe meningeal reactions and suggests that dosage over 20,000 per day is unnecessary.

The figures in the Edinburgh series are too small for subclassification to be of value, but the four recoveries received heavy penicillin dosage in various schemes of administration. (See Appendix 6). Two received no sulphonamides and the other two were given sulphathiazole and sulphadiazine respectively. The fatal cases lived 24 days on the average compared with five days in the pre-sulphonamide period and 10 to 11 days in the sulphonamide period.

Influenzal Meningitis.

One of the earliest purposes to which Fleming's original penicillin extracts were put was the inhibition of other organisms so that h. influenzae might grow. It is therefore not surprising that little was expected of penicillin in treatment of meningitis due to this organism, and it was not until 1945 that Forgacs,
Hutchinson and Rewell (1945) found improvement in the condition of a child aged 2½ years who had been treated with 30,000 units penicillin intramuscularly for 24 hours, after which h.influenzae was reported in the CSF removed on the previous day. Penicillin therapy was continued and reinforced with sulphadiazine 1.5 Gm followed by 1 Gm 4-hourly. Both were stopped on the seventh day and the CSF was sterile on the 12th day. Laboratory tests showed the penicillin sensitivity to be comparable to that of the standard Oxford staphylococcus.

Gordon and Zinnemann (1945) tested 18 strains of h.influenzae from CSF 16 were Pittman type 6 and were inhibited by 5 units penicillin per cc while a smaller proportion were inhibited by 2.5 units per cc., a concentration attainable in the CSF only by intrathecal injection. McIntosh and Drysdale (1945) recorded a case treated by intrathecal penicillin and oral sulphonamides. Relapse occurred in spite of 208,000 units of penicillin and 40.5 Gms of sulphapyridine, and a further course of 250,000 units penicillin intrathecally and 22.5 Gms "Sulphamezathine" in seven days with, in addition,1,200,000 units by intramuscular injection over 12 days. An intrathecal injection of 50,000 units of penicillin produced twitching of the face and limbs. A similar event occurred in a later case (Drysdale and McIntosh,1946) after the 11th intrathecal injection of 50,000 units. This high
dosage was used in an attempt to maintain a CSF penicillin concentration of 2 units per cc. The attempt failed and the possible advisability of using two intrathecal injections daily is suggested.

Further small series are reported by Zinnemann (1946), Gottlieb, Forsyth and Allott (1947), Gerrard J. (1947), Thomson, Bruce and Green (1947) and others, with general agreement on the necessity for heavier than normal intrathecal dosage and on the marked variations in sensitivity shown by different strains of h. influenzae. Of the four cases in the Edinburgh series, the case which recovered, received 30,000 units penicillin intrathecally daily for 3 days and 20,000 units daily for five days, in addition to rather more than the standard course of sulphathiazole. Apart from a case moribund on admission, in the other two cases the intrathecal penicillin dosage was 20,000 units daily for five or six days. One received sulphathiazole while the other received intramuscular penicillin.

Streptococcal Meningitis.

The remarks on Pneumococcal meningitis apply in general to streptococcal meningitis, as the susceptibility of streptococci (other than strep. viridans) is generally in the same range as that of pneumococci.

Smith (1947) states that intracranial abscess is more common in streptococcal meningitis than in the others. White, Murphy, Lockwood and Flippin (1945) showed one recovery in five severe cases of streptococcal meningitis.
This case was at first treated with penicillin 10,000 units intracisternally and 100,000 units intramuscularly 2 hourly for four days, the dose being halved for the next two days. The Edinburgh case which recovered, (aged 8 years) received a standard course, namely 20,000 units penicillin intrathecally daily and 100,000 units intramuscularly daily by Eudrip, both for 5 days together with sulphathiazole 24 Gms spread over nine days. The other case treated with penicillin died within twelve hours of admission.

Streptomycin.

Since its introduction in 1944, streptomycin has in this country at least, been mainly reserved for treatment of various forms of tuberculosis including meningitis. A fair number of cases of influenzal meningitis have been treated in America, and a few in this country, and the preliminary results are promising. The United States National Research Council (Keefer et al. 1946) has produced results of a series of 1000 cases including 100 of h.influenzae meningitis treated with streptomycin with or without penicillin, sulphonamides or serum. A daily dose of approximately 2 - 4 Gms intramuscularly in 4 hourly doses was accompanied by daily intrathecal injections of 25 - 100 mgm (25,000 - 100,000 units) in 5 - 10 cc saline. Cairns, Duthie and Smith (1946) report a small series including a fatal case of h.influenzae meningitis.

The two cases of h.influenzae meningitis treated
with streptomycin at Rush Green Hospital happened to be admitted to hospital at a time when a case of tuberculosis meningitis had just stopped having treatment with streptomycin. A small amount of streptomycin already made up for intrathecal injection was available and it was considered that the type of case justified its use in the circumstances. The long history of the earlier case together with the prolonged treatment with sulphonamides and penicillin seemed to indicate the need for something more effective. In view of the history the case was naturally considered at first as one of meningococcal meningitis with relapse and sulphonamide treatment was started. When the diagnosis was made and it was decided to use streptomycin, penicillin was given in heavy dosage subcutaneously as an adjuvant form of treatment. The sulphonamide dosage was already high. The penicillin was discontinued when it was found that the organism was weakly sulphonamide sensitive, insensitive to fairly high concentration of penicillin.

The second case (Case 101) also received intramuscular streptomycin. Our previous experience with a case of tuberculosis meningitis suggested that division of the dose into two twelve hourly doses should be effective. Garrod (1948) shows that once the minimum effective dose of penicillin has been passed, there is no acceleration of its lethal action on increasing the concentration of penicillin. In the
ease of streptomycin on the other hand, increase in the concentration used results (in vitro) at least) in increase in the speed of bactericidal action, and that this action is also speeded up by rise in temperature. Furthermore, if streptomycin is tested against a large inoculum there is rapid reduction in the number of viable organisms for a short time, after which the rate of fall is almost completely checked. Garrod demonstrates that this action is due neither to the exhaustion of the streptomycin nor to development of lasting resistance on the part of the surviving organisms. It thus seems possible that 12 hourly large doses providing intermittent lethal concentrations might be more effective than three hourly small doses providing a mildly bacteriostatic concentration. Garrod quotes W.H. Feldman (Trans. Stud. Coll. Phys. Phila., 14, 81) who found that when treating tuberculosis in guinea pigs, doses given once, twice or four times daily, or four times daily during alternate weeks had essentially equal efficacy.

Other Antibiotics.

It seems probable that further antibiotics will be produced which may be of value in treating the more resistant types of meningitis.

Brownlee and Bushby (1948) for instance give a table showing the sensitivity of many organisms to aerosporin, showing that h. influenzae and other Gram negative bacilli are more sensitive to this antibiotic than to streptomycin. Intrathecal injections in mice
were well tolerated, and intramuscular injections have been given to children suffering from pertussis.

Complications and Sequelae.

The question of blocks in the cerebrospinal fluid channels has already been considered. Cases of chronic hydrocephalus usually die within a relatively short period.

Zinnemann (1946) quotes a private communication from Hattie E. Alexander which sums up the position in relation to h. influenzae meningitis.

"The experience in this country when both sulphadiazine and typespecific rabbit antiserum are used in combination for the treatment of influenzal meningitis indicates that any residual damage is exceedingly rare following recovery."

The same remarks appear to apply to the other types as well. In regard to the first case of streptococcal meningitis in the Rush Green series it is not possible to be sure whether the man's present complaints are residua of the meningitis or of the cavernous sinus thrombosis. The only cranial palsy which tends to persist is a acoustic nerve deafness. (See Case 56)

From the anatomical relations one wonders whether this may be due to damage at the labyrinthine end of the nerve rather than the nuclear end or along the course of the nerve.

Rush Green Hospital Cases.

The six cases form too small a series for statistical analysis but a number of points not covered in the preceding discussion are worthy of mention. Of the two cases of pneumococcal meningitis one had a previous
history of a vague respiratory infection, the other was apparently primary. The meningitic were poorly marked in both on admission but became more evident later. Treatment was by full doses of penicillin by intrathecal and intramuscular or subcutaneous injection, and heavy doses of sulphonamides by mouth. The older girl made uneventful progress and was discharged in just over four weeks. The infant’s condition deteriorated rapidly and he died on the 8th day of disease.

Case 108 appears for the available evidence to have been a double infection with meningococci and h.influenzae. The original response to treatment was good but the relapse did not respond in the same way although the treatment appears to have kept the CSF channels free from block. It is difficult to judge whether this child would have responded without streptomycin. The slow return to normal of the CSF lymphocyte count is thought to be a result of the streptomycin rather than the meningitis.

Case 101 also showed a rapid change from polymorph to lymphocytic preponderance in the CSF. The response to intrathecal streptomycin was by no means dramatic until reinforced by intramuscular doses. The small amount of Sulpha- mezathine was given before it was known that some streptomycin would be available for intramuscular use, and probably had little effect on the outcome.
In case 102 the situation was complicated by the presence of the cavernous sinus thrombosis. An unusual feature was the lack of confusion and drowsiness although meningitic signs were well marked. The deterioration on 8th November was probably due to reduction of penicillin dosage. Penicillin in oil was used at this time but it was very painful and later experience has shown that it has no advantage over aqueous solutions given subcutaneously in rather higher dosage twelve hourly or eight hourly. (Patients also prefer this latter method to continuous intramuscular penicillin drip which was, on the other hand economical of penicillin). In this case intrathecal penicillin was not used. It will be seen that treatment was discontinued before the temperature had subsided. This was because it was almost certain that the temperature was due to the sulphonamide and / or penicillin.

In Case 103 it was considered that the weakness of the right arm was due to a localised collection of pus overlying the centre of the motor cortex, and that recovery should be complete. Unfortunately the mother has failed to bring the child for follow up.

It so happens that all the Rush Green cases had had treatment immediately prior to diagnosis of meningitis so that intravenous sulphonamides were not given as would normally have been done.
Miscellaneous Other Considerations.

Zinnemann (1946) suggests that treatment of non-fulminant h.influenzae meningitis should be concentrated in a number of treatment centres. The arguments for are self evident. The danger seems to be that such concentration of cases would deprive the less specialised hospitals of the experience on which the early diagnosis of meningitis depends. A reasonable compromise would be to have a visiting consultant with specialised knowledge of the disease who could visit cases being treated in other hospitals and advise on treatment. Should treatment beyond the capacity of the hospital concerned be required, the patient could then be transferred as necessary. (e.g. for ventricular punctures in adults etc.)

The laboratory side of the investigation requires special experience on certain points, such as the typing of h.influenzae and estimation of sensitivity, and it is considered that selected Emergency Public Health Laboratories could give valuable assistance in this direction.
SUMMARY and CONCLUSIONS.

The case notes of 93 cases of meningitis due to organisms other than meningococci and tubercle bacillus occurring in Edinburgh City Hospital for Infectious Disease between 1930 and 1946, and 6 cases seen personally at Rush Green Isolation Hospital 1946 to 1948 are analysed. A further 49 cases from 1916 onwards for which full case notes were not available are considered in less detail.

The necessity for early and detailed diagnosis and vigorous treatment is stressed.

It is noted that the advent of sulphonamides made a large reduction in the mortality of diseases formerly considered 100% fatal, and that penicillin used with sulphonamides caused a further large reduction in mortality. (Appendix 2 gives details). Streptomycin promises fair for the future of h.influenzae meningitis, and rabbit antisera when available in this country should prove helpful.

References are made to the literature in the discussion.

The present position may be summarised as follows:-

(1). The three commonest types of meningitis other than meningococcal and tuberculous meningitis are those due to the pneumococcus, h.influenzae and streptococci, but staphylococci and a very large
number of organisms can cause meningitis.

(2) There is no marked seasonal variation although rather fewer cases occur in the summer.

(3) The annual incidence bears no relation to that of meningococcal or tuberculous meningitis.

(4) Pneumococcal meningitis commonly occurs in children but may occur at any age. Influenzal meningitis usually occurs in children between three months and three years, adult cases being rare. Both are much more common in males than females. Streptococcal meningitis observes no marked age or sex preference.

(5) Mortality is greatest at the extremes of the groups.

(6) Many cases, particularly infants, do not present the typical signs of meningitis. The possibility of meningitis must be borne very much in mind where discoverable conditions do not account for the ill state of a child, especially in the presence of vague respiratory conditions, ear nose and throat infections, vomiting, convulsions. Meningitis following otitis media is more commonly streptococcal or pneumococcal. Many cases particularly those due to *h. influenzae* or pneumococcus are apparently "primary".

(7) The various types of meningitis cannot with confidence be distinguished one from another except by lumbar puncture. The course of pneumococcal meningitis is on average more rapid than the others, but any one of the three may produce a fulminating case resembling
or an indolent fulminating meningococcal meningitis. 

(8). Meticulous precautions must be taken when performing a lumbar puncture and especially intrathecal injections to avoid introduction of infection into the CSF spaces, and the contamination of specimens for laboratory investigation.

(9). To ensure prompt treatment and minimise errors due to contamination of the specimen, direct films stained methylene blue for morphology of cells and organisms and Gram should be examined immediately. Two specimens should be taken, one being placed in the incubator and the other used for cell count, direct films chemistry, and inoculation of blood again and chocolate agar plates, the latter preferably being seeded with staphylococci to assist in identifying h.influenzae.

(10). Treatment should be commenced as soon as CSF has been withdrawn for examination,

a) Sulphamezathine or sulphadiazine should be given intravenously and then by mouth in doses about 50% above those given in the M.R.C. pamphlet "The Medical Use of Sulphonamides" until the diagnosis has been made. Meningococcal meningitis does not normally require quite such high dosage.

b) The primary focus should be treated.

Operation if required should not nowadays go beyond the evacuation of pus and establishment of free drainage.
while the patient is very ill.

d) Once the diagnosis of non-meningococcal, non-tuberculous pyogenic meningitis is made, all means of attack must be used with concentration and persistence. Thus pneumococcal, streptococcal and staphylococcal cases should be given heavy dosage of sulphonamides by mouth, (2Gms 4 hourly in the adult) penicillin in doses of say 300,000 units subcutaneously 6 hourly at first and 12 hourly later (or slightly less for young children) and crystalline penicillin 20,000 units intrathecally daily for five or more days depending on the CSF findings. H. influenzae meningitis requires similar sulphonamide dosage but double penicillin dosage, while Alexander's rabbit antiserum and/or streptomycin should be used if available. The last is the most promising drug to date.

e) Organisms should, when laboratory facilities allow, be typed and tested for sensitivity against the available drugs. Forms of treatment to which the organism is insensitive may then be dropped.

e) Treatment must be continued for at least five days after the CSF has become sterile and the temperature returned to normal.

(11). Relapses should be treated as new attacks. Relapses are common in H. influenzae meningitis.

(12). Permanent sequelae are rare.

(13). The services of consultants and central laboratories should be available for points in which specialised skill is required.
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## APPENDIX 1

### CASES OF PYOGENIC MENINGITIS - ANNUAL INCIDENCE

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
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<th>Influ-</th>
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**Totals** 142  99  25  14  4

- January to September: 2
- October to December: 4

( ) Report of one case not available.
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<th>Streptococcal</th>
<th>Lobar</th>
<th>Pneumobacillus</th>
<th>S. Dublin</th>
<th>S. OeI</th>
<th>Total</th>
<th>Recovered</th>
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<td>-</td>
<td>46</td>
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<td><strong>25</strong></td>
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<td><strong>1</strong></td>
<td><strong>142</strong></td>
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</table>
SEASONAL INCIDENCE  E.C.H  APPENDIX 3

PNEUMOCOCCAL MENINGITIS

- JAN  FEB  MAR  APR  MAY  JUN  JUL  AUG  SEP  OCT  NOV  DEC
- 16  21  26  31  36  41  46

H. INFLUENZAE MENINGITIS

- JAN  FEB  MAR  APR  MAY  JUN  JUL  AUG  SEP  OCT  NOV  DEC
- 16  21  26  31  36  41  46

STREPTOCOCCAL MENINGITIS

- JAN  FEB  MAR  APR  MAY  JUN  JUL  AUG  SEP  OCT  NOV  DEC
- 16  21  26  31  36  41  46
AGE & SEX INCIDENCE AND RECOVERIES

A - PNEUMOCOCCAL MENINGITIS - E.C.H.

B - H. INFLUENZAE MENINGITIS - E.C.H.

C - STREPTOCOCCAL MENINGITIS - E.C.H.
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<tr>
<th>Case No</th>
<th>Name</th>
<th>Sex</th>
<th>Age</th>
<th>Years</th>
<th>Months</th>
<th>Days of Disease on Admission</th>
<th>Days in Hospital</th>
<th>Total</th>
<th>Result</th>
<th>Temp. on Admission</th>
<th>Pulse</th>
<th>Respiration</th>
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</tbody>
</table>

### Summary of Clinical Features

- **History and Examination**

- **Signs**
- **Positive**
- **Negative**

- **Examination**
- **Neurological**
- **Mental Status**
- **Neck**
- **Neck Response**
- **Abdominal**

- **Laboratory**

- **Investigations**

- **Other**

### Appendix

- **Pneumococcal Meningitis**
- **Pneumonia**
- **Pneumothorax**
- **Pneumoperitoneum**

### Notes

- **specify any additional notes or comments**

---

*Please review the table and notes for detailed clinical and examination findings.*
## PNEUMOCOCCAL MENINGITIS

### Summary of Treatment

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<th>Pen</th>
<th>Sulfol.</th>
<th>Other</th>
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</tr>
<tr>
<td>9</td>
<td></td>
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</table>

### Subtotal

- Pyr = Pyrimethamine; Pen = Penicillin; Sulfol. = Sulfoxycycline; Other = Other antibiotics

### Treatment Regimens

- *Note: For cases 1-8, refer to the chart for specific treatment regimens.*

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- For cases 9-10, refer to the chart for specific treatment regimens.

### Notes

- Pyrimethamine 25mg IM daily
- Penicillin G 2.5mL IM daily
- Sulfoxycycline 1mL IM daily
- Other antibiotics as per case notes
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<th>Day of Disease</th>
<th>Lumbar CSF Removed</th>
<th>Appearance</th>
<th>Protein</th>
<th>Polymorphs</th>
<th>Lymphocytes</th>
<th>Red Blood Cells</th>
<th>Subsequent Punctures</th>
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**APPENDIX 6 (cont.)**

**SUMMARY OF LUMBAR, CISTERNAL AND VENTRICULAR PUNCTURES.**

**PNEUMOCOCCAL MENINGITIS**

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<tr>
<th>Day of Disease</th>
<th>Lumbar CSF Removed</th>
<th>Appearance</th>
<th>Protein</th>
<th>Polymorphs</th>
<th>Lymphocytes</th>
<th>Endothelial Cells</th>
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**Notes:**
- CP: Blood vessel entered.
- CP3: cloudy deep brown bloody fluid.
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<th>Antimicrobial Agent</th>
<th>Dosage (mg/kg)</th>
<th>Duration (days)</th>
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<tr>
<td>Trimethoprim</td>
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Summary of Treatment

**MB Pyr** = Sulphonamide; **Tria** = Trimethoprim; **Diaz** = Diazotetrazine; **Pen** = Penicillin; **G** = Gentamicin

---

**APPENDIX G**

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<th>Pen</th>
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**APPENDIX H**

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**APPENDIX I**

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<td>Antimeters of Disease</td>
<td>Day of Disease</td>
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**Notes:**
- Poly, L, E, Prot, S, Chi, Whit indicate the presence of specific characteristics.
- Turbid, Hazy, Turbid (blood), etc., indicate the appearance of the sample.
- + and ++ indicate varying degrees of presence.
- N, Clear, Opaque, Bloodstained, etc., indicate the condition of the sample.
- Turbid, Parulent, etc., indicate the type of reaction.

**Appendix 6 (cont).**
SKELETON TEMPERATURE CHARTS OF SELECTED CASES

\[ \begin{align*}
\text{P}_{\text{im}} & = \text{Penicillin intramuscularly.} \\
\text{P}_{\text{sc}} & = \text{Penicillin subcutaneously.} \\
\text{P}_{\downarrow} & = \text{Penicillin intrathecally.} \\
\text{Str}_{\text{im}} & = \text{Streptomycin intramuscularly.} \\
\text{Str}_{\downarrow} & = \text{Streptomycin intrathecally.} \\
\text{S} & = \text{Sulphonamides.} \\
\text{L}_{\downarrow} & = \text{Lumbar puncture.} \\
\text{C}_{\downarrow} & = \text{Cisternal puncture.} \\
\text{V}_{\downarrow} & = \text{Ventricular puncture.}
\end{align*} \]
CASE 19
E.H. Male 13 yrs
PNEUMOCOCAL MENINGITIS

TEMPERATURE (° FAHRENHEIT)

Pulse

Resps

Day of Ill
CASE 22
HC Male 36
PNEUMOCOCCAL MENINGITIS

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CASE 67
E.H. Female 1½ yrs
H. INFL UENZAE MENINGITIS

(Chart showing respiratory rates over time with measurements in beats per minute.)
Case 78
A.N. Female 3 yrs
H. INFLUENZA Meningitis

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H. influenzae meningitis
CASE 101
T.C. Male 17 yrs
H. INFLUENZAE MENINGITIS
APPENDICES 8 & 9

DATES OF LUMBAR PUNCTURES ETC. IN RELATION TO DAY OF ONSET AND DATE OF START OF TREATMENT

Pneumococcal Meningitis

- O DAY OF ONSET
- X LP BEFORE ADMISSION
- □ LP, CP, VP

H. Influenzae Meningitis

Streptococcal Meningitis

Other Meningitides
### APPENDIX

#### COMPARISON OF VARIOUS ASPECTS OF THE THREE GROUPS.

<table>
<thead>
<tr>
<th></th>
<th>Pneumococcal</th>
<th>Influenzal</th>
<th>Streptococcal</th>
</tr>
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<tbody>
<tr>
<td>Cases in 30 yr Period</td>
<td>99</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>Aver Annual Incidence</td>
<td>3.3</td>
<td>0.87</td>
<td>0.48</td>
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<tr>
<td>Peak Annual Incidence</td>
<td>(1940-1)</td>
<td>(1944)</td>
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<td>50% younger than yrs.</td>
<td>10</td>
<td>1</td>
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<tr>
<td>Males % of cases</td>
<td>64.6</td>
<td>64</td>
<td>50</td>
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<tr>
<td>Cases 1930 - 1946</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>58</td>
<td>20</td>
<td>12</td>
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<tr>
<td>Males % of cases</td>
<td>69</td>
<td>70</td>
<td>50</td>
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<tr>
<td>Day of Disease on Adm.</td>
<td>2 - 3</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Temperatures on Adm.</td>
<td>101</td>
<td>100.8</td>
<td>99.9</td>
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<tr>
<td>Neck Rigidity %</td>
<td>92</td>
<td>90</td>
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<td>Head Retraction %</td>
<td>31</td>
<td>16</td>
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<td>Opisthotonos %</td>
<td>8.6</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Kernig negative %</td>
<td>15.5</td>
<td>8</td>
<td>17</td>
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<tr>
<td>Knee jerks negative %</td>
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<td>-</td>
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<td>Abd. Reflex negative %</td>
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<td>56</td>
<td>50</td>
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<tr>
<td>Retention of Urins %</td>
<td>12</td>
<td>-</td>
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<td>Strabismus %</td>
<td>10</td>
<td>8</td>
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<td>Convulsions %</td>
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<tr>
<td>Day of Disease</td>
<td>3</td>
<td>4 - 5</td>
<td>7</td>
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<tr>
<td>Almost Clear - Hazy, %</td>
<td>15.5</td>
<td>4</td>
<td>53</td>
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<td>Opalescent %</td>
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<td>76</td>
<td>75</td>
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<td>Turbid</td>
<td>53</td>
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<td>75</td>
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<tr>
<td>Thick</td>
<td>8.6</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Prot Min Aver (Max. mgm %)</td>
<td>46(1120)</td>
<td>75(300)</td>
<td>1500</td>
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<td>Gluc Min Aver (Max. mgm %)</td>
<td>13.2(64)</td>
<td>10(27)</td>
<td>10</td>
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<tr>
<td>Chl. Min Aver (Max. mgm %)</td>
<td>554(738)</td>
<td>622(773)</td>
<td>606</td>
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<td>Cases</td>
<td>10 40 8</td>
<td>5 11 4</td>
<td>5 5 2</td>
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<td>3 5 3</td>
<td>7 5 ?</td>
<td>8 8 -</td>
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<tr>
<td>Survived to day number</td>
<td>5 10 2</td>
<td>12 31 ?</td>
<td>12 34 -</td>
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ANNUAL DEATHS - VARIOUS DISEASES.

APPENDIX 11

TUBERCULOSIS OF C.N.S., SCOTLAND

NON-MENINGOCOCCAL MENINGITIS - SCOTLAND

MENINGOCOCCAL MENINGITIS - SCOTLAND

NON-MENINGOCOCCAL MENINGITIS MIDLOTHIAN

PYOGENIC MENINGITIS - E.C.H.
NOTIFICATIONS CEREBRO-SPINAL FEVER
SCOTLAND 1906 - 1940
DEATHS VARIOUS CAUSES 1931-1945
APPENDIX 13

BY MONTHS.
DEATHS - SCOTLAND AND E.C.H.
NON-MENINGOCOCCAL MENINGITIS
BY AGE & SEX.

DEATHS - NONMENINGOCOCCAL MENINGITIS - SCOTLAND - 1931 - 1945
MALE
FEMALE

DEATHS - PYOGENIC MENINGITIS - EDINBURGH CITY HOSPITAL - 1916 - 1946
MALE
FEMALE
FIGURES IN PURPLE RELATE TO EDINBURGH CITY HOSPITAL
Deaths - Scotland 1931-1945
Meningococcal Meningitis
by Age and Sex

Appenix 15
DEATH RATES - ALL CAUSES
BY SEX AND AGE GROUPS
SCOTLAND - 1938 (BEING
CENTRE YEAR OF PERIOD 1931-1943).
**Comparison of Male & Female Deaths in Scotland 1931-1945 from All Causes & from Nonmeningococcal Meningitis**

(Female deaths expressed as percentage of male deaths)
### Relative Frequency of Various Kinds of Infective Meningitis in Children

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<th></th>
<th>T.B.</th>
<th>Men.</th>
<th>Inf.</th>
<th>Ph.</th>
<th>Str.</th>
<th>Sta.</th>
<th>&amp;c.</th>
<th>Total</th>
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<td>1920 - 1931</td>
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<td>160</td>
<td>78</td>
<td>69</td>
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<td>39</td>
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<td>1933 - 1936</td>
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<td>51</td>
<td>38</td>
<td>36</td>
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<td>36</td>
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<td><strong>Children's Hospital</strong></td>
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<td>Washington, D.C.</td>
<td>205</td>
<td>180</td>
<td>100</td>
<td>73</td>
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<td>5</td>
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<td>Health, New York.</td>
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<td>209</td>
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<td><strong>Hospital for Sick Children</strong>,</td>
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<td>Sick Children, Sidney</td>
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<td>86</td>
<td>38</td>
<td>13</td>
<td>78</td>
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- T.B. - Tuberculous Meningitis
- Men. - Meningococcal do.
- Inf. - H. Influenzae do.
- Ph. - Pneumococcal do.
- Str. - Streptococcal do.
- Sta. - Staphylococcal do.
- &c. - Other forms of do.