INTRATHECAL PENICILLIN IN THE TREATMENT OF MENINGOCOCCAL MENINGITIS

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PREFACE.

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CONTENTS.

CHAPTER I.

HISTORICAL ACCOUNT.

In the following pages a historical account of the disease and its treatment has been given. Numerous articles were consulted and frequent reference was made to the classical survey of the disease by E. Ashworth Underwood (1940).

Cerebrospinal fever has been defined as an infectious, contagious disease occurring both sporadically and in epidemics, and caused by the meningococcus (Diplococcus meningitidis of Weichselbaum).

Epidemics of this disease have swept Europe and America at well recognised intervals, the first accurately recorded epidemic, occurred in Geneva in 1805, and was desribed by Vieusseux. His account (quoted from Foster and Gaskell 1916) is of interest, and corresponds closely with disease as it is known today. For example he states: "The initial symptom was a sudden failure of strength, the expression was anxious, the pulse feeble, sometimes threadlike, in a few cases hard and bounding. There was violent headache in the main frontal. The headache was followed by vomiting of green matter, by stiffness of the spine, and in some by convulsions. The body showed livid patches/

patches after death, occasionally during life".

After this first epidemic in Geneva, the disease was reported as occurring in other countries. America was affected and eventually the United Kingdom but not until a comparatively late date. Hirsch in his work, "Treatise on Geographical and Historical Pathology", described four epidemic periods.

The first period, 1805 - 1815, involved Geneva, America and France.

The second period, 1837 - 1850, involved Gasconey, Italy and America.

The third period, 1854 - 1875, involved Sweden, Germany, Russia, Greece, Ireland and America.

The fourth period, 1876 - 1886, involved Cape Town, Poland and England.

To these four periods Sir Humprey Rolleston (1919) added a fifth, starting in 1902 and continuing to the present day.

The first outbreak in the United Kingdom occurred in Ireland, in the Belfast and Dublin workhouses in the year 1846, followed in the year 1866 by an epidemic in Dublin of a more virulent type.

Scotland enjoyed immunity until the year 1877 - 78 when thirty four cases occurred in Dundee which were reported on by Dr. MacLagen in 1886. Kilmarnock had a slight outbreak in 1884, but there was no major outbreak until the beginning of this/

this century, when simultaneously with the outbreak in Belfast of 1906-7, cases occurred in Glasgow.

The cases in this epidemic appeared at first in a sporadic manner, and it was not until the following Spring, when conditions were favourable for dissemination, that the disease assumed epidemic proportions. According to Currie and Macgregor (1908) the first case was admitted to a Glasgow Fever Hospital in May, 1906, and from then on they occurred at about the rate of one case per month. During the first six months of 1908 eight hundred and two cases were registered, but the epidemic waned in the second half when only one hundred and ninty six cases were reported.

Following this main outbreak, sporadic epidemics occurred up and down the country, and in view of its prevalence and infectivity it was decided in 1912 to make notification compulsory. In the result, an accurate record of the incidence of the disease in subsequent years is available. The return of the Registrar General shows that, after an abrupt rise from 300 or 400 cases in each of the years 1913 and 1914 to an average combined service and civilian figure of nearly 2,500 cases annually during the war years, the epidemic prevalence gradually diminished, until, by 1921, they had reverted to prewar level. Since then however, there has been a gradual though not continuous increase, and the same tendency has been observed/

observed in other European countries. In 1939 there was again a marked increase in the numbers, which reached epidemic proportions by 1940.

The importance of the "carrier", combined with overcrowding and unhygenic surroundings, in favouring the spread of the disease was realised at a fairly early date. Flugge in 1906 found that 70 per cent of the people in close proximity to a case harboured the organism in the nasopharynx, but few of these carriers developed the disease. During 1915, 690 carriers were reported to the Medical Research Committee and of these only two developed the disease. Yet the importance of the carrier in spreading the disease is illustrated again and again in different epidemics. For example, Reece writing on the 1914 epidemic, stated that the first civilian case to occur in this country was that of a nurse known to have been in the company of a Canadian soldier who, on being swabbed, proved to be a carrier. (Quoted from Worster-Drought and Kennedy 1919). Again, Chalmers (1930) writing on the epidemic of 1906, states that the disease would appear to have been propagated among healthy carriers so that when the climatic conditions favourable for promoting catarrhal conditions and creating pressure on house room recurred in the later winter months, recurrences of the disease in individual wards became frequent.

It is apparent from the statistics of the earlier epidemics/

epidemics that cerebrospinal fever was a disease of a fatal nature which did not readily respond to treatment and it was not until the closing years of last century, and the beginning of this, that advances in therapy were made. The beneficial effect of lumbar puncture as a therapeutic measure was recognised during the epidemic in Portugal of 1901-03. However, it was not until Flexner and Jochmann, two independant workers, in 1905 produced a serum having a bactericidal effect on the meningococcus that the first real advance was made.

Flexner, in a report on 1294 serum treated cases, states that he had 400 deaths, a fatality rate of 30 per cent. He advocated the earliest possible use of serum following diagnosis, and his results showed that when serum was injected intrathecally within the first three days the mortality rate fell to 18 per cent. Between the 4th and 7th days, it was found to be 27 per cent and when later than this date 36.5 per cent.

It was hoped that results in this country would be equally good but they varied to a very great extent and were on the whole disappointing. Currie and Macgregor (1908) during the 1906-08 Glasgow epidemic treated 105 cases with serum and 205 without serum. The mortality rate for the serum-treated was 64.8 per cent and for the non-serum 79.5 per cent. Their conclusions were that serum-therapy did not have any marked results over the first 10 days of illness, but following on this/

this period the serum-treated cases did have a better chance of life. They believed that serum-therapy, although failing to avert the disease, hampered its progress by aiding the natural defences of the body and discouraging the formation of exudates which might retard recovery. During the 1915 epidemic, disappointing results were again obtained. Surgeon General Rolleston (1915) in a series of serum-treated cases found that his mortality rate was 61 per cent and Foster and Gaskell in a similar series had a mortality rate of 55 per cent.

Rolleston's figures were as follows:-

	Cases.	Deaths.
1st to 3rd days	70	60 per cent.
4th to 7th days	24	58 " "
later than 7th	11	72 " "

In 1915 Gordon discovered that there were four types of meningococci and made their recognition possible by means of specific agglutinating sera. These types were used for the production of immune sera. Subsequent work showed that these 4 groups did not embrace all meningococci and also that cross agglutination occurred. The differentiation of the type was not easy, as the agglutinations were difficult to perform, and satisfactory suspensions difficult to obtain. When the type of meningococcus was known the univalent serum as pointed out by Banks (1931) gave good results and this was particularly the case/

case with Group 1.

It was generally accepted that the failure of serum therapy arose from the difficulty of preparing a potent antiserum for the different strains of the meningococcus occurring in the epidemics. Thus Underwood (1932) writing of the epidemic in Rotherham in 1931 states:-
"The great drawback to treatment during this outbreak was the impossibility of obtaining a potent anti-serum, due of course, to the fact that the sera used for some months after the start of an epidemic must be prepared from inter-epidemic strains which often differ markedly from those actually prevalent during the epidemic".

Ferry, Norton and Steele (1931) found that filtrate from young cultures of the 4 recognised Gordon types contained extra-cellular toxin specific to the 4 types, as well as strains, common to all. Thus animals injected with the toxin developed specific antitoxins. Ferry considered that the toxins were largely responsible for the symptoms of cerebrospinal meningitis and by the intrathecal injection of the toxins in monkeys gave rise to symptoms similar to those resulting from the injection of living cocci. These symptoms were modified by adding the corresponding anti-toxin to the toxin before injection.

In 1933 a number of cases were treated in the London County Council Hospital with Ferry's meningococcal antitoxin and these have been reported by Banks (1935). In a series

of 25 cases the fatality rate was slightly better than the standard fatality rate of 30.9 per cent given by Flexner for his series of cases up to 1913. The conclusion drawn by Banks was that, the meningococcal anti-toxin prepared by using as antigens soluble toxins of type 1, 2, 3, 4, meningococci, appeared to be particularly potent for types 1 and 3.

Walsh (1938) however, reviewed 23, 685 American cases occurring between 1920 and 1936 and concluded there was no evidence that the use of serum had lowered the fatality rate in recent years.

Thus serum-therapy was not a success and it was left to chemotherapy to open a new era in the treatment of this deadly disease.

CHEMOTHERAPY.

The first worker in the science of chemotherapy was Ehrlich who commenced in 1904 a search for a drug to cure syphilis. In the same year Koch attempted to cure septicaemia by the intravenous injection of drugs, but this was not successful. Research on these lines, however developed for the next forty years until in 1935 it was found that the sulphonamide group, although weak disinfectants in vitro had a very good protective action in vivo. Domagk then discovered that the dye prontosil red protected mice against large doses of haemolytic streptococci, and that it had a curative effect

in/

in such infections. This was followed by Trefouel, Nitti and Bovet, showing that sulphanilamide produced a similar action and being a simpler derivative was more advantageous to use than the more inert substances.

Buttle and his co-workers (1936), and Proom (1937), demonstrated the protective and curative effect of sulphanilamide in the treatment of meningococcal infections in mice.

The following year Roche and McSweeney (1939) in Dublin started to treat cases with, prontosil album orally, soluseptasine intramuscularly, and serum intrathecally; their mortality rate in a series of 52 cases was 57.14 per cent.

Crawford and Fleming (1938) reported a series of 10 cases which they had treated with prontosil album, orally, intramuscularly, and intrathecally, and they had only one death.

Banks (1938) reviewed a series of 113 cases of which 38 were treated with intravenous and intrathecal serum, 59 with serum and sulphamilamide, and 16 with sulphanilamide alone. His fatality rate in those treated entirely with serum was 16 per cent, and the cerebrospinal fluid was found to be sterile in the majority of cases within 24 to 48 hours.

The fatality rate in the serum and sulphanilamide treated was less being 11.8 per cent, and the fluid sterile in 24 hours. In the 16 cases treated entirely with sulphanilamide there was only one death.

In/

In 1938 Smith, Maxson and Murphy in a series of 157 sulphanilamide and intravenous antitoxin treated cases had a death rate of about 12.5 per cent which was lower by about 25 per cent than when intrathecal serum and sulphanilamide was given. Eldhal (1938) treated 12 cases of meningococcal meningitis in children under 4 years of age with intrathecal and intramuscular injections, of a 5 per cent solution of sulphanilamide. The amount injected into the spinal canal being from 5 to 30 cc. according to the amount of cerebrospinal fluid withdrawn. The mortality rate was 18 per cent as compared to his previous rate of 70 per cent for children of the same age group with other forms of treatment.

Hobson and McQuaide (1938) in an investigation for a drug of low toxicity but with a bacteriostatic power equal to or greater than that of sulphanilamide, easily attained by oral or parentral administration, selected sulphapyridine which according to Whitby, (1938) was shown to have a bacteriostatic action on the meningococcus equal to that of sulphanilamide. Wein had also shown, that in mice and rats, this drug had a quarter of the toxicity of sulphanilamide, and did not produce porphyrinurea or other drug changes in the haemopoietic system which were associated with sulphanilamide.

In their investigation Hobson and McQuaide (1938) found that the sulphapyridine passed rapidly from the blood stream into the cerebrospinal fluid where it was found in approximately 50 per cent of the blood concentration.

Effective/

Effective bacteriostasis was achieved by a concentration of not more than 3 mgm per 100 cc., which could be obtained readily by the administration of smaller doses than would be required for sulphanilamide. It also had a beneficial action in pneumococcal infections. Sulphanilamide requires a level in the body fluids of 5-10 mgm per 100 cc., to be effective which demands the taking of large doses.

Somers, (1939) during an epidemic in the Sudan, reported that he had treated 143 cases of meningococcal meningitis solely with small doses of sulphapyridine and his mortality rate fell to 10 per cent. In all cases the drug was administered intrathecally and also either intraperitoneally or intramuscularly.

Bryant and Fairman (1939) working under similar conditions treated a series of 168 cases, with M & B 693, and had only 8 deaths.

In 1943 and 1944 two large scale studies were made on the treatment of Cerebro-spinal Fever, one in Scotland and the other in England and Wales. The Scottish one was made by the Scientific Advisory Committee of the Department of Health in which 2,223 cases received by 7 hospitals in 1936 to 1941 were reviewed. In the second, Beeson and Westerman (1943) analysed 3,375 cases reported by more than 100 Hospitals to the Ministry of Health during 1939-41. Both surveys included the epidemic of 1940. The gist of their findings was that sulphonamides had/

had materially reduced the case fatality, that nothing was to be expected from serotherapy as an adjuvant to chemotherapy and that big doses and early administration of sulphonamides were less important than the host factor, particularly the patient's age, in determining the outcome.

The patients treated with sulphapyridine far outnumbered those treated with other drugs, of which sulphanilamide and sulphathiazole were the chief. In Scotland a sufficient number were treated with the last two drugs to enable some comparison to be made. Rather surprisingly it was found that sulphanilamide, of which the bacteriostatic power was said to be the lowest, produced the best results as judged by fatality rate and length of stay in hospital, but gave the highest number of complications.

MORTALITY.

From the historical account it can be seen that cerebro-spinal fever from the time it was first recognised has had the reputation of being a singularly fatal disease, and yet the severity varied in the differnt epidemics. It was shown that an epidemic may be highly virulent in one localised area, while nearby, the disease may be epidemic but of a more benign type. Walsh (1938) in America recording the experience of 20,000,000 urban dwellers found that in the period 1920-36 the fatality/

Fig 1. :- Death-Rate for Cerebro-spinal Fever in Glasgow.
1911-1944.

fatality rate varied in the different municipalities from 67.7 per cent to 38.1 per cent.

The degree of severity of the infection is of importance. The most severe cases are generally at the start of an epidemic tapering off towards the end. The sporadic type of case is as a rule milder than those occurring in an epidemic.

The age of the patient is of paramount importance, and it has been found that the fatality rate is highest at the extremes of life, a fact which chemotherapy has not altered. For infants of one year of age the fatality rate has been found to be six times as great as that in young adults, and for people over the age of 60, ten times as great.

The sex of the patient has been shown to have no influence on the incidence of fatal cases.

With regard to the duration of illness before admission to hospital, it has been found by the Scottish Scientific Advisory Committee, from their recent large scale survey in 1944, that the duration of illness before admission to hospital and the institution of therapy was of secondary importance if the delay did not exceed one week.

The fatality rates in Glasgow for cerebrospinal fever from 1911 to 1944 have been charted on the opposite page. (See Fig. I opp.). The marked decrease which occurred in 1938 and 1939/

1939 onwards corresponds with the introduction of the sulphonamides.

PENICILLIN.

With the increase in the quantity of Penicillin released for general use, and the very favourable reports which were forthcoming on the results obtained from its uses in other forms of infection, it was decided to try its effect in the treatment of meningococcal meningitis. The greatest success was obtained in the treatment of Gram positive organisms but its bacteriostatic effect on the meningococcus had already been proved by Fleming and other workers. In the following pages a brief resume of the history and relevant findings are given.

Professor Fleming (1929) noted that a mould produced a substance which inhibited the growth, in particular, of staphylococci, streptococci, gonococci, meningococci and the Corynebacterium diphtheriae. He suggested its use as an inhibitor in the isolation of certain types of bacteria especially H.influenzae. He also noted that the injection into animals of broth containing the substance was no more toxic than the same quantity of broth used for growing the mould and that it might be a useful antiseptic for application to infected wounds.

The/

The mould from which the substance was obtained was Penicillium notatum. It is a species of the common genus Penicillium which occurs widespread on organic material. It rots fruit, attacks meat and vegetables and is used in industry for ripening cheese. There are about one hundred species known.

The gross appearance is that of a bluish green mould like that seen on Stilton cheese - a species of the same genus. The vegetative mycelium consists of a complex network of branching thin walled, septate hyphae. The characteristic of the genus is the penicillus or a sexual reproductive organ.

Penicillin, which is a complex substance of unknown chemical structure is obtained from the mould. It occurs naturally as an unstable acid. In the form of alkaline earthy salts, it is stable between pH.5 and 7. The preparations used therapeutically are the calcium and sodium salts.

The molecule is small which may be the cause of its rapid excretion. Penicillin is soluble in ether, chloroform, and amyl acetate. The salts are extremely soluble in water. It is destroyed by dilute acids, alkalies and prolonged heating. It is inactivated by oxidising agents, procaine, heavy metals especially zinc, cadmium, copper and mercury, primary alcohols, ketonic reagents and enzymes produced by certain bacteria.

In/

In the dried state the anti-bacterial activity remains undamaged for a long time. Activity lasts longer at temperatures below 10°C.

Florey and his colleagues (1941) adopted a unit of antibacterial activity. This unit was purely arbitary and corresponded to the potency of a certain sample of concentrated penicillin. It roughly corresponded (Fleming 1946) to the amount of penicillin which when dissolved in 50 millilitres of broth, would just inhibit the growth of the test staphylococcus, and was known as the "Oxford Unit". When more penicillin was obtained the Oxford Unit was established as an International unit containing 0.0006 milligramme of pure crystalline sodium salt of penicillin II.

Pure penicillin would have an activity of about 1000 units per milligramme. Commercial products of the type used were only 30 to 50 per cent pure. The impurities consist mainly of pyrogenes.

It has been shown by Abraham, Chain, and other workers (1941) that in the presence of penicillin, even in low concentrations, certain species of bacteria not only cannot multiply, but slowly die. This effect is exerted as well in serum, blood and even pus, as it is in a simple medium such as broth. It is independent of the number of bacteria present. Even/

Even in high concentration penicillin has no effect on the leucocytes. In contrast the sulphonamides are toxic in high concentration, act best in the presence of a few bacteria, and are inhibited by the breakdown products in pus. Bigger (1944) pointed out that penicillin and sulphonamides acting together produced an enhanced effect.

Most of the susceptible species of bacteria are Gram positive. They include the three main pyogenic cocci (staphylococcus, pneumococcus, and streptococcus pyogenes) the gas gangrene group, B. anthracis and the C. diphtheriae.

The only fully susceptible Gram negative species are Neisseria, the gonococcus and meningococcus.

Among resistant organisms are the tubercle bacillus and almost all Gram negative bacilli including the coli-typhoid-dysentery group, the genera Brucella and Haemophilus, and two common invaders, B. proteus and B. pyocyaneus.

As regards its absorption and excretion it has been found that penicillin is absorbed rapidly from muscle and wounds, slowly from subcutaneous tissue. It is absorbed from the small intestine, but not from the mouth or rectum.

After intramuscular injection, as has been demonstrated by Fleming and other workers, (1944) penicillin can be detected in the urine almost immediately and persists from 6 to 24 hours. There is an immediate rise in the blood concentration to a peak, followed by a rapid fall. They found that the time at which

penicillin/

penicillin disappeared from the blood was as follows:-

Intramuscular Dose.	Time of Disappearance.
15,000	2 to 3 hours.
20,000	3 "
35,000	4 "
50,000	4 to 5 "
100,000	5 to 6 "

The maximum concentration which Fleming obtained in the blood after 15,000 units is less than after 100,000 units, and it is clear that if the interval between the injections is kept the same, then the larger the dose, the higher will be the average penicillin content of the blood. It was found that when single injections were used a bacteriostatic level can be obtained in the blood much more economically by the use of smaller doses like 15,000 units than with larger doses of 100,000 units. Six doses of 15,000 units given every two hours will certainly maintain a bacteriostatic power in the blood for 12 hours, and this only makes 90,000 units, whereas 100,000 units in a single dose will last only for 5 or 6 hours.

Rammelkamp and Keefer (1943) demonstrated that penicillin does not pass through the blood-spinal fluid barrier in significant quantities following the intravenous injection of the substance in normal adults. Similarly Herrell (1944), after administering 30,000 units intravenously to a patient with/

with a healthy central nervous system, was unable to detect any penicillin in the fluid removed thirty and sixty minutes after injection.

McDermott and Nelson (1945) examined the cerebrospinal fluid of 70 patients after the intramuscular injection of 300,000 units of penicillin, and found that only a trace was present.

Rammelkamp and Keefer (1943) have shown that when penicillin is injected intrathecally it is slowly absorbed from the subarachnoid space. Following the intrathecal injection of 5,000 to 10,000 units it could be detected in the spinal fluid 31.5 hours afterwards. They found that the rate of absorption in patients suffering from meningitis was greater but that the penicillin could still be detected 24 hours later. With regard to the effect of disease on the blood-cerebrospinal fluid barrier, Rosenberg and Sylvester (1944) have shown that, penicillin administered to patients suffering from meningitis either intravenously or intramuscularly in adequate dosage is excreted into the cerebrospinal fluid. The dosage they used was from 20,000 to 40,000 Florey units, and from 60 to 140 minutes later penicillin was found in the spinal fluid in concentrations varying from 0.05 to 0.35 units per cc. These findings were confirmed by Cooke and Goldring (1945). Rosenberg and Arling, (1944) after the treatment of their series of/

of cases of meningococcal meningitis with penicillin, advocate its use intramuscularly or intravenously in addition to intrathecal injection.

A remarkable feature of penicillin is its low toxicity even in high concentrations in the human body, which is in contrast with other chemotherapeutic agents, most of which require to be given in doses approaching the toxic level before the desired effect is obtained.

Florey and his colleagues (1941) demonstrated this lack of toxicity on the living cell in vivo, on animals and in humans. He and Jennings (1942) further showed as did also Hamre and her colleagues (1942) that, the higher the purity of a penicillin preparation the lower was its toxicity. Fleming and his colleagues (1944) were able to raise the blood concentration to a level 1,000 times greater than that required for therapeutic purposes, without there being any toxic manifestations.

The penicillin manufactured in this country must pass a toxicity test before being marketed. The Pharmacopoeia require the penicillin salts to have a potency of not less than 300 units per milligramme and the Therapeutic Substances Act forbids the issue or use of a product of lower potency.

The products issued by manufacturers vary in potency from 300 to about 1,500 units per milligramme. However the lethal dose of the products of different manufacturers varies widely. Welch/

Welch and his colleagues (1944) believed that the toxicity which resulted from the use of salts of a high degree of purity was due almost entirely to the cation, and that pure sodium penicillin was scarcely more toxic than sodium acetate containing the same weight of sodium.

One of the most frequent toxic manifestations was pain following intramuscular injection. This has been shown by Herwick and his colleagues (1945) to vary inversely with the purity of the salt used.

An American survey (1943) of 500 cases reported local thrombophlebitis as having occurred in 19 cases after intravenous administration. Other toxic reactions reported were urticaria in 14 cases, and in others, mild chills and fever.

The most sensitive tissues to impurities in penicillin are those of the central nervous system.

Rammelkamp and Keefer (1943) showed that the intrathecal injection of 10,000 Florey units in a normal person was followed by headache, vomiting, increased intrathecal pressure and pleocytosis in the spinal fluid. In subjects with meningitis they found that no untoward symptoms were noted following the injection of 3,000 to 10,000 units. Rosenberg and Arling (1944) noted that the cases which had doses up to 15,000 units of penicillin intrathecally or had the dose repeated every twelve/

twelve hours had more severe and persistent headache, their fever was also more prolonged and the signs of meningitis retracted slowly. The question of the toxicity of intrathecal penicillin is discussed more fully in a later chapter.

Professor Fleming (1943) was the first to treat a case of meningitis with penicillin. The infecting organism was a streptococcus which was resistant to sulphonamide. Penicillin was given intrathecally in 4 doses of 50,000 units and also intramuscularly. The total amount given was 1,627,800 units intramuscularly and intrathecally 22,500 units. Progress was uninterrupted and he was discharged from hospital five weeks from the beginning of treatment.

After Fleming's successful treatment of this case, other workers reported success, particularly in the treatment of pneumococcal meningitis with penicillin.

In America, Waring and Smith (1944) described a series of 12 cases of pneumococcal meningitis of which 4 recovered. On the other hand, Sweet and his colleagues (1945) did not have such satisfactory results. They reported a series of 16 cases in which they had only 7 recoveries. Applebaum and Nelson (1945) also did not have results comparable to those of Waring and Smith. For a series of 67 cases of pneumococcal meningitis they had only 26 recoveries. Smith, Duthie and Cairns (1946) report a greater degree of success. In a series of 38 cases of pneumococcal/

pneumococcal meningitis they had only 9 deaths. The cases were divided into two lots of 19. The first lot were treated with penicillin alone and the second lot with penicillin and sulphadiazine. In those treated with penicillin alone there were 7 deaths as compared with 2 in the other group. However 3 of the patients in the first lot were in a moribund condition on admission and died a few hours afterwards. Of their fully treated patients 2 died from intracranial abcess, whilst in the remaining 2 the initial response was good but subarachnoid block developed with subsequent relapse and death.

In the second group treated with penicillin and sulphadiazine, one patient died from fat embolism, and one other died within 12 hours of admission to hospital. Relapses were more frequent in those cases treated with penicillin alone.

Rosenberg and Arling (1944) treated 65 patients suffering from meningococcal meningitis with intrathecal and intravenous or intramuscular penicillin. They had 64 recoveries. Their cases were practically all young adults, the age group in which the most favourable results are obtained. Some of the cases however were severely ill on admission being in a comatose state or convulsing. They concluded that penicillin administered both intrathecally and systemically is an effective, highly potent agent, in the treatment of meningococcal meningitis.

CHAPTER II.

In this chapter, the plan of experiment, the details of treatment, and a clinical survey of the cases, are recorded.

PLAN OF EXPERIMENT.

In March 1945, when supplies of penicillin became more plentiful it was decided to try its effect in the treatment of cases of meningococcal meningitis admitted to Ruchill Fever Hospital. As already noted in the introduction, penicillin has a bacteriostatic effect on the meningococcus and pneumococcus, and beneficial results have followed its use by other workers. All the cases dealt with in this work were under the age of five years, the age group in which the disease occurred most frequently and one in which the fatality rate is very high.

Theoretically there were many points in favour of the use of penicillin. For example the dosage was accurate and administration was easy which was a favourable factor in dealing with cases, particularly infants, where vomiting or an easily upset gastro-intestinal system had to be combated. In addition the depression, cyanosis, or effects on the haemopoietic system frequently associated with sulphonamide therapy would not be encountered.

It was initially intended to treat one hundred cases with penicillin alone but the results obtained did not justify continuing the experiment beyond the first fifty cases. Whereupon it was decided to try the effect of a combined penicillin and/

and sulphonamide therapy in a further fifty cases and to compare the results in both groups.

The penicillin treated cases were collected over the period ranging from March 1945 until January 1946 and those in the sulphonamide and penicillin treated group from February 1946 until May 1946. All the cases were of sporadic occurence, but during the winter months as might be expected, the disease became more prevalent and this was particularly the case from the end of November until the end of March.

The degree of severity of the cases was assessed in both groups, and classified as severe or moderate. Extreme care was taken in this assessment, the greatest difficulty being encountered with borderline cases, but the fact that the division was only into two major groups reduced the degree of error which might arise with a more numerous classification.

In the severely ill category were placed all the cases in which there was clinical evidence of a severe infection as judged by the attitude and mental condition of the patient, and associated symptoms such as convulsions, severe headache, nuchal rigidity, head retraction, opisthotonus, a positive Kernig's sign, irritability, listlessness, and pallor. A petechial eruption when present was regarded as an indication of a severe infection.

In the moderately ill group were placed patients who had moderate/

moderate toxaemia with generally slight nuchal rigidity, and a positive Kernig's sign. A petechial eruption was not found in the moderately ill patients.

The fifty patients in the series who were treated with penicillin alone are referred to as Group A., and the fifty treated with a combination of penicillin and sulphonamide as Group B.

The distribution of the cases with regard to the degree of severity of illness is shown in Table No. 1 set forth below.

TABLE NO. 1 - DISTRIBUTION OF CASES WITH REGARD TO DEGREE OF SEVERITY OF ILLNESS IN GROUPS A & B.

	MODERATELY ILL.	SEVERELY ILL.
GROUP A.	No. of Cases. 14	No. of Cases. 36
GROUP B.	No. of Cases. 18	No. of Cases. 32

A fortunate feature with regard to the comparison of the Groups A and B is that they contain a similar number of severely ill patients.

DETAILS OF METHOD OF TREATMENT.

The ward in which the patients were treated is divided into four compartments, the first two of which were reserved for those in the acute stage of the disease, one for adults and/

and older children and the other for the cot cases, younger children and infants. The remaining two compartments were reserved for patients at the convalescent stage. Generally after the first week, when the acute stage was passed, the cases were promoted through to the third compartment, and in the last week to the fourth compartment.

On admission the patient was at first briefly examined in the ambulance to exclude the possibility of the presence of any other infectious disease, and was then directed to the ward. In the ward the temperature, pulse and respiration rates were recorded and the patient was bathed.

Within half an hour of admission the patient was given a thorough clinical examination and an estimation of the degree of severity of illness made. After this a lumbar puncture was performed. It was found that the easiest way to perform this operation was to have the patient placed in the left lateral position, and the spine flexed by a nurse who passed one hand round the child's neck and the other round the knees drawing them up towards the chin, then clasping both hands in front. A local anaesthetic was dispensed with as it was found to obscure the intervertebral spaces, and the degree of discomfort was not any more than would result from the injection of a local anaesthetic. After thorough cleansing of the skin in the lumbar region with methylated spirits and iodine, a

lumbar/

lumbar puncture needle was passed into the spinal canal between the 3rd and 4th lumbar vertebrae in a slightly upward direction. In children the theca is penetrated usually at a depth of from $\frac{1}{2}$ to $\frac{3}{4}$ of an inch. The increased feeling of resistance which the dura offers in adults is not apparent to the same extent in children, so that it was found useful after penetrating the ligamentum flavum, to remove the stilette from time to time, as the needle is pushed in until the theca is penetrated and the fluid drops out. The amount of fluid withdrawn varies according to the intracranial pressure, gauged according to the rate of flow and the tension of the anterior fontanelle. In cases under markedly increased pressure and in infants with bulging fontanelles up to 20 c.c. were withdrawn, but the usual quantity was from 10 to 15 c.c. This usually reduced the rate of flow from the needle to an approximately normal one.

The following observations on the cerebrospinal fluid were made every 48 hours and recorded.

(1) Its macroscopic appearance, whether turbid, opalescent or clear.

(2) Pressure.

(3) Total cell count.

(4) Differential cell count.

(5) Type of organisms on direct film examination.

(6) The bacteriostatic titre of the fluid.

MACROSCOPIC APPEARANCE./

MACROSCOPIC APPEARANCE.

The naked eye appearance of the cerebro-spinal fluid withdrawn from the subarachnoid space varied in transparency from slight to complete opacity. In this series of cases distinction has been drawn between fluids perfectly colourless and transparent - called clear, fluids which were practically clear but with a ground glass appearance,- called opalescent, and fluids which were definitely opaque, whitish in colour, yielding on standing a deposit of pus-called turbid.

In Group A (treated with penicillin alone) 48 cases on admission had turbid, and 2 had opalescent cerebrospinal fluids. In Group B (treated with sulphonamide and penicillin) all 50 cases had turbid fluids on admission.

PRESSURE.

An estimation of the pressure from the rate of flow was made, the average normal rate being about one drop in every two or three seconds. It was difficult to assess the pressure in this way as crying or struggling which was frequent in children of this age group tended to give a high reading. The method of recording the pressure was as follows:-

The normal pressure was taken as 30 drops per minute and one plus (+) indicated an increase of pressure to about 60 drops per minute and (++) a practically constant flow. The latter/

Total Cell Count of Cerebro-spinal Fluid.

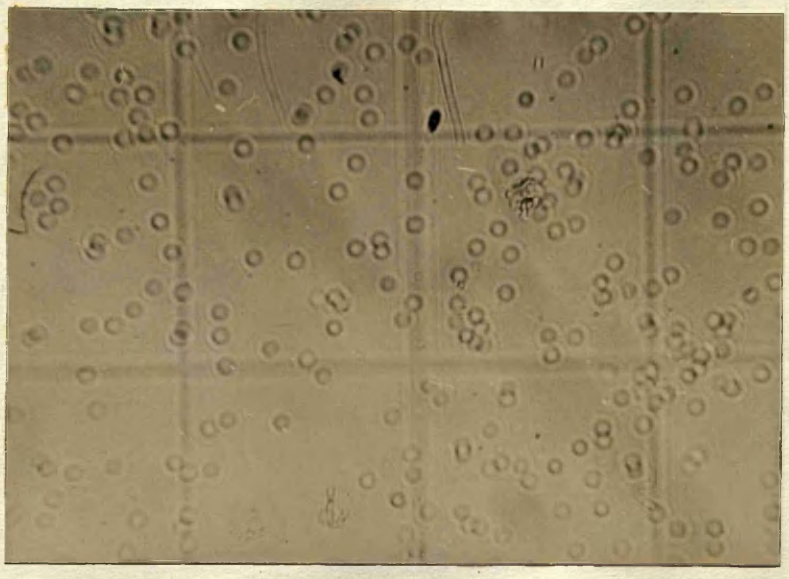


PLATE I: Showing marked increase in cell-count during first week of illness. [x 400]

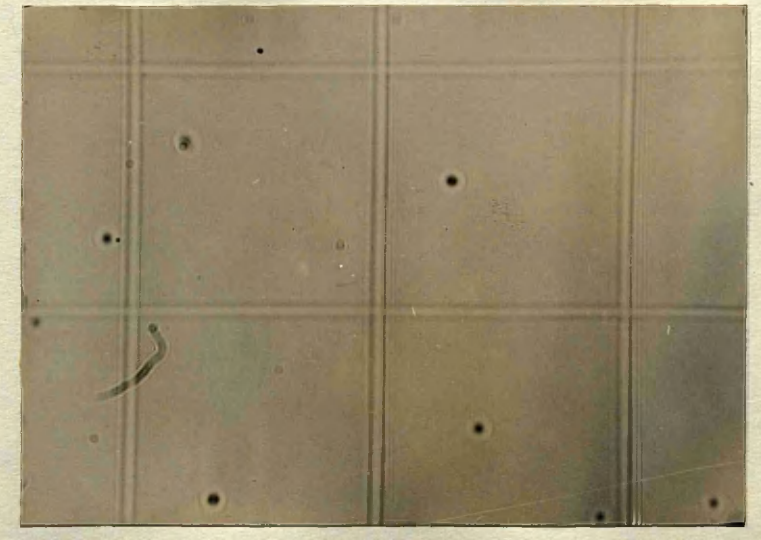


PLATE II: Showing cell-count of above case during second week of illness [x 400]

latter pressure was the more frequent finding. As the fluid was withdrawn the pressure fell steadily until it dropped to an approximately normal rate, at which point the operation was discontinued.

TOTAL CELL COUNT.

It was important that a total cell count should be taken as soon as possible after withdrawing the fluid, or the cells would have adhered to the sides of the tube, thus giving low counts. The apparatus employed was the Fuchs - Rosenthal counting chamber and an ordinary white cell counting pipette.

The fluid without diluting was drawn up into the clean dry pipette and then introduced in the usual manner below the coverslip over the central ruled area. The count was made with the low power lens of the microscope, all the cells in the ruled area being counted. This ruled area corresponds to 3.2 c.m.m. and to obtain the approximate number of cells per c.m.m. the total count was divided by 3. At the initial lumbar puncture, where the fluid was distinctly turbid and the total cell count very high, it was recorded as 1,000 plus cells per c.m.m. In the second week of illness the number of cells in the cerebrospinal fluid decreased more rapidly. (See plates I and II)

DIFFERENTIAL CELL COUNT OF CELLS IN CEREBRO-SPINAL FLUID.

The proportion of polymorphonuclear leucocytes to lymphocytes/

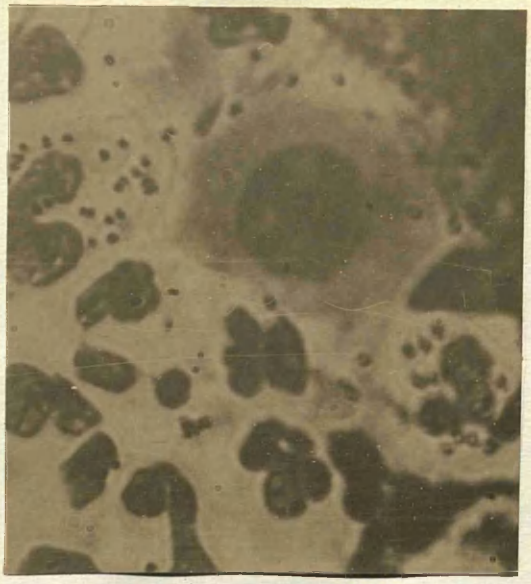


PLATE III: Stained film of cerebro-spinal fluid on admission.
[Note abundance of meningococci] *[X 1000]*

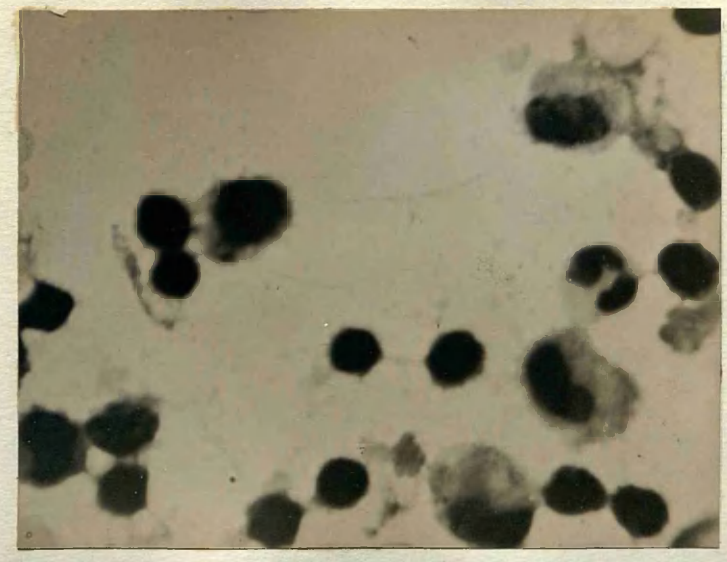


PLATE IV: Stained film of cerebro-spinal fluid 48 hours after administration of Penicillin, 50,000 units, intrathecally.
[Note. No growth obtained on cultures] *[X 1000]*

lymphocytes was ascertained from the stained film. One hundred cells were counted and the number of each type present recorded.

TYPE OF ORGANISM - DIRECT FILM.

The films were made from the centrifugilised deposit of the fluid, and stained by Gram's method whereafter they were examined under the oil immersion lens to determine the type of organism present. It is believed, and was also noted in this study, although no note was made of the proportion of extracellular to intracellular, that in the more severe and long standing cases there is a higher proportion of extracellular meningococci.

In all the cases in both groups A and B definite evidence of a meningococcal infection was obtained by finding the organism either in a direct film, on culture, or in both direct film and culture. Cases in which the infecting organism was not identified were not included in this study. The meningococcus was not found in any of the cases in either group 48 hours after the intrathecal administration of the penicillin.

(See Plates III and IV opp.)

CULTURE.

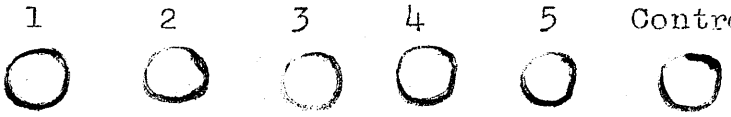
A small amount of the sediment was inoculated on to Chocolate Agar medium. This was then incubated at 37°C for 18 to 24 hours and the resulting growth studied. Films were prepared and stained by Gram's method. Subcultures were made on to serum agar slopes from which the biochemical reactions were/

were noted.

BACTERIOSTATIC TITRE.

The method employed for determining the bacteriostatic titre of the cerebrospinal fluid was as follows:

To each of a series of sterile stoppered tubes - (3 ½ inch) 0.5 c.c. of varying concentrations of the cerebrospinal fluid was added as shown diagramatically below.



BROTH.	-	.5c.c.	.5c.c.	.5c.c.	.5c.c.	.5c.c.
CEREBROSPINAL FLUID.	.5 c.c.	.5c.c.	.5c.c.	.5c.c.	.5c.c.	.5c.c. discarded
STANDARD SUSPENSION OF FLOREY STAPHYLOCOCCUS.	1 drop	1 drop	1 drop	1 drop	1 drop	
DILUTION.	neat	½	¼	⅛	1/16	

The dilutions were made in sterile broth and were prepared with graduated pipettes as in serological tests involving the preparation of a series of doubling dilutions; pipettes used were sterile, the usual technique being adopted to ensure the sterility of all the materials employed. A control tube containing 0.5 c.c. of broth was included in the series. To each tube was then added a large loopful (standard loopful of 3 mm. diameter), of a 1 in 300 dilution (in broth) of a twenty-four hours' broth culture of a standard strain ("Oxford H") of Staphylococcus aureus.

The/

Bacteriostatic action of cerebrospinal fluid during penicillin treatment.

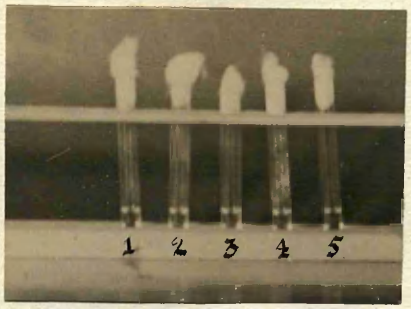


Plate I:- Normal Tubes Before Incubation.

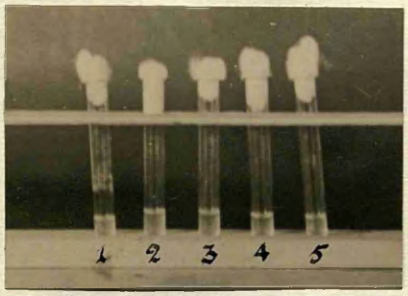


Plate II:- Tubes Showing No Inhibition at any Dilution
i.e. Growth in All Tubes.

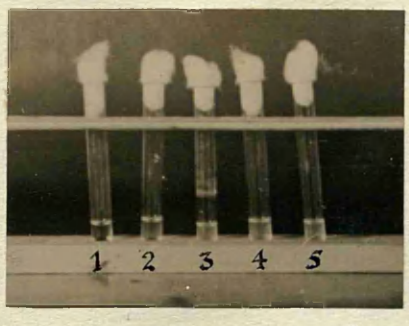


Plate III:- Tube 1: Complete Inhibition - [Neat Serum]
* Tube 2: Doubtful Inhibition [Dilution 1/2]
Tube 3: No Inhibition [Dilution 1/4]
Tube 4: No Inhibition [Dilution 1/8]
Tube 5: No Inhibition [Dilution 1/16]

* This tube would be sub-cultured on a suitable medium.

The tubes were incubated for eighteen to twenty-four hours, when readings of the resulting growth, or absence of growth, were made according to the visible turbidity or absence of turbidity.

In this way the bacteriostatic level of the cerebrospinal fluid was determined within twenty-four hours. If necessary these results were confirmed or checked by taking a loopful from each tube after thorough shaking of the contents, and by making single stroke inoculations in paralled on a 4-inch plate of blood-agar, the position of each stroke being indicated by dividing the outside of the plate into divisions with grease pencil. The plate accommodated six such divisions, one for the stroke inoculation from each tube. The presence or absence of growth in the tubes and the relative amount of growth when there was a partial inhibition was thus conclusively determined after twenty-four hours' incubation of the plate. Plates I, II, and III illustrate the method of recording the results.

BLOOD EXAMINATION.

Having carried out a full investigation of the cerebrospinal fluid, the blood was investigated with regard to culture and qualitative and quantitative changes of the leucocytes.

BLOOD CULTURE.

It is difficult in children to get blood from the arm or leg as a result of the chubbiness of their limbs and the minuteness/

minuteness of the veins in children of 5 years of age and under. In infants below the age of one year, it was comparatively easy to obtain blood from the saggital sinus through the anterior fontanelle. This method was resorted to in every case below the age of one year unless the veins in the arms or legs offered good prospect of success from venepuncture. The amount of discomfort and risk of introducing infection were no greater than with a venepuncture provided a proper aseptic technique was adhered to. It was customary to have the scalp shaved over the anterior fontanelle and for a surrounding area of 2". This part was thoroughly cleansed with spirit and iodine, whereupon a hypodermic needle was introduced through the scalp at an angle of about 60^{o}. Slight back pressure was exerted on the plunger as the needle was slowly inserted in the mid line of the posterior angle to a depth of about $\frac{1}{8}$" - when the saggital sinus was usually entered. The quantity of blood withdrawn was as a rule 5 c.c. and this was introduced into a bottle containing Hartley's broth to which had been added to prevent the inhibiting action of penicillin or sulphonamide, Thioglycollic and Aminobenzoic acids respectively.

DISMISSAL LUMBAR PUNCTURE.

If the patient had made satisfactory clinical progress, and had completed the convalescent stage of 14 days, a lumbar puncture was performed with a view to determining the condition of/

of the cerebrospinal fluid as a criterion of the complete elimination of infection. In the first instance it was important to note that the pressure was normal from the point of view of excluding incipient hydrocephalus. If the pressure was normal and the cell count below 12 cells per c.m.m. and the protein content normal, the case was considered cured and allowed home.

TREATMENT.

The cases as already stated were treated with penicillin alone (Group A) or with a combination of penicillin and sulphonamide, (Group B).

PENICILLIN TREATED CASES.

The penicillin used in the experiment was the sodium salt prepared chiefly by Messrs. Boots and Glaxo laboratories. It was obtained either in small bottles containing 100,000 units or in tablets of 10,000 units. The potency of the preparations used varied between 300 to 500 units per milligramme. A solution with a concentration of 10,000 units was obtained by dissolving 100,000 units in 10 cc's of sterile water. Strict asepsis was observed in the preparation of the solution. As the bottles were fitted with rubber stoppers, easily perforated with a hypodermic needle, this enabled the solution to be prepared without the contents being exposed to the atmosphere. The dose which was injected intrathecally every second day in the/

the Group A cases was 50,000 units, i.e. 5cc of penicillin solution. This was believed to be the most appropriate dose considering the fact that it was introduced only on each alternate day, i.e. at intervals of 48 hours. A smaller dosage of 10,000 units would require to be injected daily, and it was the intention in giving the larger dose to introduce a quantity which would have a prolonged bacteriostatic effect. The solution was prepared before the lumbar puncture was performed so that it was ready for introduction to the spinal canal. In cases which were proved not to be meningitis, having clear fluids under normal or slightly increased pressure, the penicillin was returned to the refrigerator and stored there until required. If there was the slightest doubt from the macroscopic appearance of the fluid that the diagnosis might be one of meningitis, the penicillin was injected, and the diagnosis established exactly later from an investigation of the fluid. Having withdrawn from 10 to 15 cc.'s of fluid which, from its macroscopic appearance suggested meningitis, 5 cc. of the prepared solution of penicillin was drawn into a sterile syringe, the nozzle of which fitted into the end of the lumbar puncture needle. Some cerebro-spinal fluid was drawn back into the syringe to ensure that the needle was properly in the canal, and also to dilute and warm the penicillin, which was then slowly injected. The plunger was drawn back slightly once or twice. With the plunger right/

right down to the bottom of the syringe the needle and syringe were withdrawn. A collodion patch was then placed over the puncture wound.

The cases in Group B received both penicillin and sulphonamide. The dose of intrathecal penicillin which was administered was 30,000 units of sodium salt every 48 hours prepared in sterile water as already described in the treatment of the Group A cases. It was decided to reduce the dose to 30,000 units as a result of the toxic symptoms which developed in infants following the administration of 50,000 units. The sulphonamide used was sulphapyridine and the scale of dosage is shown in Table No. 2 below.

TABLE NO. 2 - SHOWING SCHEME OF DOSAGE.

Age period in years	0-2 yrs.	2-5 yrs.
Initial Dose in Grms.	1	1.5
Dose in Grms., thereafter every 4 hours.	0.5	0.5
Total Dosage during first 24 hours in Grms.	4	5

After the first dose the amount of sulphonamide administered was reduced to 0.5 grms. The drug was administered with sodium bicarbonate in milk and the number of cases in which it had to be changed as a result of sickness was very few.

An/

An adequate fluid intake was maintained at all times. Administration of the sulphonamide was at four hourly intervals for the first seven days and thereafter three times a day for the next four or five days dependent on the progress of the case.

The termination of therapy followed on the disappearance of the manifestation of the disease and on a marked improvement being found in the cerebro-spinal fluid. It was found that these conditions were usually satisfied at an earlier date in the penicillin and sulphonamide treated group than in those treated with penicillin alone, but this is discussed in detail in a later chapter.

DIET.

The diet was mainly fluid during the first two days of the illness. For infants, four hourly feeds of glucose and sterile water were given, the quantity depending on the age of the child. For older children the diet given was as full as was consistent with the digestive capacity. As a rule the digestive functions are not greatly disturbed in cerebro-spinal fever and the appetite is often well maintained. In the early acute stages milk, beef essence, tea, toast, chicken soup and custards were given. In the convalescent stage a more normal diet was given particularly fish dishes and chicken, or with infants milk or bread and milk mixture. Throughout the treatment the/

the children were encouraged to drink, and a plentiful supply of bland drinks was maintained for this purpose, orange juice being a particular favourite.

RELIEF OF SYMPTOMS.

For the relief of headache aspirin, or phenacetin and caffeine, were found effective - a dose of 5 grains being sufficient for the older children. Restlessness and convulsions were treated with Syrup of Chloral. Infants received a dose of 30 minims and older children one drachm.

It was found that the quickest way to relieve vomiting due to the cerebrospinal fever was to perform a lumbar puncture. In addition an intraperitoneal saline was of value in children in whom there was evidence of dehydration.

As with most febrile diseases, constipation was the general rule particularly in the older children. To counteract this a soap and water enema was given on every second day during the acute stage. In addition Castor Oil or Syrup of Figs was administered.

CLINICAL SURVEY.

The general aspect of the patient on coming under observation was as follows. He lay in bed usually on his side, with the limbs in an attitude of flexion but with the head somewhat extended. Pallor was a marked feature and tended in a/

a few hours to alternate with flushing. Mental irritability was in most cases pronounced, and any interference on the part of the observer was resented, particularly if an attempt was made to place him in the supine position. The commonest symptom which heralded the onset of the disease was vomiting. The distribution of the cases in both groups which exhibited this symptom is shown in Table No. 3.

TABLE NO. 3 - INCIDENCE OF VOMITING IN BOTH GROUPS OF CASES.

GROUP.	NO. OF CASES.	VOMITING.
A	50	38
B	50	31

The vomiting tended to be projectile in character and occurred independent of, although it was aggravated by, meals. In the great majority of cases it soon ceased after lumbar puncture. The cases in which it had been present for some time were dehydrated and were given intravenous glucose saline if this were possible. If intravenous fluid could not be given, normal saline was administered intraperitoneally. In infants 6 to 8 ozs. were given and in older children up to 12 ozs. Vomiting of this explosive, projectile type, was a useful diagnostic sign when associated in particular with other manifestations of the disease, such as nuchal rigidity, or Kernig's sign, for it helped to draw the parents and the practitioner's/

practitioner's attention to the seriousness of the illness.

HEADACHE.

In children over the age of two years a complaint of headache and stiffness of the neck as in adults was frequent. The headache was usually occipital and radiated down the back. The severe headache associated with the disease is believed to be due to the impairment of the cerebral circulation produced by the increase of intracranial pressure (Foster and Gaskell 1916) Lumbar Puncture was noted to give relief.

NUCHAL RIGIDITY.

This was a very constant sign and was present in all cases in varying degrees, from slight stiffness of the neck muscles to definite spasm with rigidity and head retraction. By placing the hand beneath the patient's head and endeavouring to draw it upward, a definite resistance was encountered so that the chin could not be made to touch the chest. This nuchal rigidity was due to the increase in tone of the neck muscles, which arose as a result of the irritation of their nervous control.

KERNIG'S SIGN.

This sign depends on the stiffness of the muscles of the back of the thigh. The limb, when the thigh is flexed to a right angle with the trunk cannot be fully extended at the knee joint. This sign was present in practically every one of the cases but it was not considered of such diagnostic importance as/

as nuchal rigidity, and this was particularly so in children below the age of two years, in whom there is a physiological rigidity of the thigh muscles which may yield a positive sign. (Worster-Drought and Kennedy 1919).

PETECHIAL RASH.

This sign appeared in the majority of cases as a few isolated spots on the abdomen, or on the hands and feet especially on the extensor surfaces. The lesion was petechial and varied in size from that of a pin head to a lentil. The colour varied from bright red to purple and did not fade on pressure. Table No. 4 shows the number of cases in each group having a petechial rash.

TABLE NO. 4 - CASES DEVELOPING A PETECHIAL ERUPTION.

GROUP.	NO. OF CASES WITH RASH.
A	22
B	19

BACTERAEMIA.

It was not possible to obtain a sample of blood in several cases, particularly in young children with poor veins, and a closed anterior fontanelle, which prevented access to the saggital sinus. However blood for culture was obtained from 75 patients and not one was found to have a positive blood culture. A/

A possible explanation for this is that the cases dealt with were of a sporadic type and did not have a haemorrhagic rash which is associated with the fulminating type of case in which a positive blood culture is more frequently found. If, as is at present believed, the portal of entry to the meninges is by the blood stream then it would appear that this must occur at a very early stage in the illness, usually before the case is diagnosed, or admitted to hospital.

CONVULSIONS.

An epileptiform type of convulsion was present on admission in a few cases and this was found to be of grave prognostic significance.

TEMPERATURE.

The temperature recorded on admission was variable and no criterion of severity. In some very ill patients there was only a slight elevation, while in moderately ill patients it was high. As the patients condition improved it gradually assumed a normal level.

PULSE.

This was also a variable finding and was generally very rapid being particularly easily upset in children. Rates of about 160 beats per minute were a frequent finding, but as the disease process was overcome the pulse returned to normal, and it was noted to do so in all cases before the temperature dropped.

HERPES./

HERPES FEBRILIS.

Herpes febrilis occurred in 4 cases in Group A and in one case in Group B. It developed on an average from the second to the fourth day of illness and was confined to the lip margin. The first sign of its appearance was the presence of an erythematous patch on which small groups of vesicles developed. These rapidly increased in size and became purulent. It is unusual to have herpes develop in children under the age of two years. However, one of the cases in this series, aged 20 months, developed herpes in the 4th day of illness. Table No. 5 shows the distribution of the cases with herpes.

TABLE NO. 5.

CASE.	AGE.	DAY OF APPEARANCE.	RESULT.	GROUP.
1 R.B.	5	4th Day.	Cured.	A
2 W.D.	3	3rd "	"	
3 J.J.	2½	7th "	"	
4 C.C.	2	2nd "	"	
5 J.R.	4	3rd "	"	B

The presence or absence of herpes is of no prognostic significance. Formerly it was believed to be a favourable sign but cases exhibiting it quite often die. (Worster-Drought and Kennedy 1919). All the cases in this series recovered.

CHAPTER III.

THE COMPARISON OF THE CASES TREATED IN GROUPS A AND B.

Before the results which were obtained from the use of the two forms of therapy, penicillin alone, and penicillin and Sulphonamide could be compared, it was necessary to determine whether the cases treated were similar. In comparing the cases in the two groups A and B the following factors were considered.

(1) Age.

(2) Sex.

(3) The duration of illness before the commencement of therapy.

(4) The presence or absence of convulsions.

(5) The presence or absence of coma.

AGE.

All the cases considered in this work were patients of five years of age or under. The youngest patients treated in Groups A and B were aged six and four weeks respectively. It is unusual for cerebrospinal fever to occur in children below the age of two months. Rolleston and Ronaldson (1940) quote Root as being only able to collect a series of 7 such cases.

The number of patients in whom the disease occurred in a particular age group in both series of cases correspond very closely. For example in Groups A and B there were 9 and 11 cases respectively in the six months and under age group. The majority/

majority of cases occurred in children below the age of two years. In Group A they comprised 70 per cent and in Group B 68 per cent.

Table No. 6 set forth below shows the distribution of the cases in the relative age groups.

TABLE NO. 6.

THE DISTRIBUTION OF THE CASES WITH REGARD TO AGE IN BOTH GROUPS A AND B.

	Group A.	Group B.
Age.	No. of Cases.	No. of Cases.
6 Months and Under.	11	9
1 Year.	7	10
2 Years.	17	15
3 Years.	6	8
4 Years.	6	4
5 Years.	3	4
Total.	50	50

It is fortunate that the age distribution of the cases in both groups corresponded closely, for the age of the patient in cerebrospinal fever is of major prognostic significance.

SEX./

SEX.

In Group A there were practically twice as many males affected as females, the numbers being 32 males and 18 females. In Group B the distribution was more even, there being 29 males and 21 females. The sex of the patient has been found, however, to have very little influence on prognosis and confirmatory evidence of this was obtained in both series of cases. The difference in the fatality rates between males and females in either Group A or B was not more than about 1 per cent. Table No. 7 set forth below shows the distribution of the sexes in both series of cases.

TABLE NO. 7.

THE DISTRIBUTION OF THE SEXES IN GROUPS A AND B.

	Group A.		Group B.	
Sex.	No. of Cases.	No. of Deaths.	No. of Cases.	No. of Deaths.
Male.	32	10 (31.2)	29	4(13)
Female.	18	6 (33.3)	21	3(14)
Total.	50	16	50	7

Figures in brackets are percentages.

THE DURATION OF ILLNESS BEFORE THE COMMENCEMENT OF THERAPY.

In both Groups A and B there were six cases admitted in their first day of illness. The greatest number of cases in both groups was admitted in the second and third days of illness. For example in Group A there were 18 and 16 cases admitted in their second and third days of illness respectively, whilst the corresponding numbers in Group B were 27 and 9 cases. On the succeeding days in both groups, there was a comparable number admitted the only difference of note being in the fifth day when 3 cases were admitted in Group A and none in Group B.

Table No. 8 below shows the distribution of the cases according to the duration of illness before they were admitted.

TABLE NO. 8.

THE DISTRIBUTION OF THE CASES WITH REGARD TO THE DURATION OF ILLNESS BEFORE ADMISSION.

	Group A.	Group B.
Days ill before Therapy was Commenced.	No. of Cases.	No. of Cases.
1	6	6
2	18	27
3	16	9
4	3	3
5	3	0
5-10	4	5
Total.	50	50

THE PRESENCE OR ABSENCE OF CONVULSIONS.

Some patients on admission had convulsive seizures which tended to recur particularly in the cases in which the illness progressed to a fatal termination. . The convulsions occurred suddenly without any warning, attention being first drawn to the child when there were twitchings of the arms, legs and jaw. The head was held rigid, the face cyanotic and congested, and towards the end there was frequently slight vomiting.

With the return of consciousness the cyanosis passed off, marked pallor remaining. Convulsions also occurred in patients who were in a semi-comatose state, but only the cases in whom it appeared as a separate feature of the disease are considered here.

Table No. 9 below shows the distribution of the cases having convulsions on admission in their relative age groups.

TABLE NO. 9.

THE DISTRIBUTION OF THE CASES HAVING CONVULSIONS ON ADMISSION IN THEIR RELATIVE AGE GROUPS.

	Group A.	Group B.
Age of Patient.	No. of Cases.	No. of Cases.
1 Year & Under.	5	5
2 Years & Under.	3	1
3 Years & Under.	1	0
Total.	9	6

There were 9 cases in Group A and 6 Cases in Group B who had convulsions on admission to hospital. Out of the 9 cases in Group A 8 were aged up to 2 years, while in Group B they were all in this category. The remaining patient in Group A was three years of age. Convulsions occurring in children with cerebrospinal fever was of grave prognostic significance, and in Group A its incidence was higher by 6 per cent than in Group B.

THE PRESENCE OR ABSENCE OF COMA.

The children discussed under this heading were in a semi-conscious state but were capable of being roused on stimulation. They were not in true coma and could be made to swallow their drug and fluids. They lay immobile, and on one side in the characteristic attitude of a severe case of meningitis, having marked nuchal rigidity which in some cases had progressed to retraction or opisthotonus. The arms were well flexed at the elbows, with the hands clasped under the chin, and the legs extended and stiff with a positive Kernig's sign. The eyes were closed, the pupils dilated, in most cases equal, and reacting sluggishly to light. Irritability on stimulation was a marked feature. Table No. 10 shows the distribution of the cases in coma with regard to age.

TABLE NO. 10.

THE DISTRIBUTION OF THE CASES IN A COMATOSE STATE ON ADMISSION.

	Group A.	Group B.
Age of Patient.	No. of Cases.	No. of Cases.
1 Year and Under.	2	2
2 Years and Under.	2	2
3 Years and Under.	1	0
4 Years and Under.	1	0
Total.	6	4

In Group B there were 4 cases in a comatose state on admission and they were all in the two years of age and under group. In Group A 4 out of a total of 6 cases were in this age group. The remaining 2 cases were aged three and four years respectively. In Group A the incidence of the comatose state was higher by 4 per cent than in Group B.

In some cases convulsions occurred in patients who were admitted in a semi-comatose state and the distribution of the cases in both groups manifesting these features of the disease is shown in Table No. 11 set forth below.

TABLE NO. 11.

THE DISTRIBUTION OF CASES IN GROUPS A AND B WHO HAD CONVULSIONS ON ADMISSION AND WERE IN A COMATOSE STATE.

Age of the Patient.	Group A.	Group B.
	No. of Cases.	No. of Cases.
1 Year and Under.	2	2
2 Years and Under.	2	1
Total.	4	3

All the cases in a comatose state on admission and having convulsions were aged two years or under. There were 4 such cases in Group A and 3 in Group B.

CONCLUSIONS.

The cases in groups A and B have compared favourably in most of the factors considered. The age distribution and the duration of illness before being admitted to hospital were similar. There were certainly 9 more cases admitted in group B in their second day of illness than in group A, but there was a similar increase of 7 cases admitted in the third day of illness in group A. Thus taking the number of cases admitted in their first three days of illness, when the fatality rate was found to be high, 40 were in group A and 42 in group B.

In group A the number of cases having convulsions exceeded those in group B by 3. Similarly there were 2 more cases admitted in a comatose state in group A than in group B. The number of cases who exhibited both convulsions and a comatose state was higher by one in group A.

These manifestations of the disease were exhibited by a very severely ill patient in whom the prognosis was correspondingly grave. Thus it would appear that a slightly greater number of patients in group A were more dangerously ill than in group B. However this difference was slight and should not have influenced to any considerable extent the results of the treatment employed.

CHAPTER IV.

CHAPTER IV.

THE COMPARISON OF RESULTS OBTAINED FROM THE USE OF PENICILLIN ALONE IN GROUP A CASES, AND THE COMBINATION OF PENICILLIN AND SULPHONAMIDE IN GROUP B CASES.

In this chapter the results obtained from the treatment of Group A cases with penicillin alone, and the treatment of Group B cases with penicillin and sulphonamide, are compared.

Special reference is made to the following factors:-

(1) The results obtained from the two forms of therapy in the different age groups.

(2) The duration of the illness before therapy was commenced and its influence on the fatality rate.

(3) The rate of resolution of the disease process as indicated by the total and differential cell counts of the cerebrospinal fluid which were done on alternate days.

(4) The duration of pyrexia.

(5) The occurrence of complications and sequelae with special reference to Hydrocephalus.

THE RESULTS OBTAINED FROM THE TWO FORMS OF THERAPY IN THE DIFFERENT AGE GROUPS.

The majority of the patients treated in both Groups A and B were under the age of two years, the age group in which the fatality rate was always high. Beeson and Westerman (1943) in their survey of cases occurring between June 1939 - June 1941 found their figures for this group showed a fatality rate of 31 per cent; six times as great as that for young adults. Similarly the Scottish Scientific Advisory Committee in an analysis of cases occurring/

occurring in the period 1936 - 41 found that the fatality rate in infants of one year of age was 28.3 per cent.

In Table No. 12 below, the distribution of the cases, in both series A and B, in their respective age groups with fatality rates are shown.

TABLE NO. 12.

THE DISTRIBUTION OF THE CASES IN GROUPS A AND B IN THEIR RELATIVE AGE GROUPS WITH FATALITY RATES.

	Group A.		Group B.	
Age.	No. of Cases.	No. of Deaths.	No. of Cases.	No. of Deaths.
6 Months & under.	11	6 (54)	9	4 (44)
1 Year	7	5 (71)	10	2 (20)
2 Years	17	1 (5.8)	15	1 (6.6)
3 Years	6	2 (33.3)	8	0 (-)
4 Years	6	2 (33.3)	4	0 (-)
5 Years	3	0 -	4	0 (-)
Total	50	16 (32)	50	7 (14)

(Figures in brackets are percentages.)

The fatality rate was high in both Groups A and B for children of six months and under. In Group A it was 54 per cent and in Group B 44 per cent. In children aged from six months to one year the fatality rate in Group A (the penicillin treated group) was 71 per cent, as compared with 20 per cent in Group B (the penicillin and sulphonamide treated group). The fatality rate in children/

children aged from one to two years was in Group A 5.8 per cent and in Group B it was 6.6 per cent. This was the only age group in which the fatality rates were more or less equal. In children in the three or four years old group, the fatality rate was again high, in the penicillin treated cases, it was 33.3 per cent but in the penicillin and sulphonamide treated cases there were no deaths. In children of four or five years of age there were no deaths in either group A or B.

Thus in all the age groups with the exception of children of two years of age, the fatality rate in the penicillin treated group was much higher than in the penicillin and sulphonamide treated group. In the 50 cases treated by penicillin alone it was 32 per cent as compared with 14 per cent in those treated with sulphonamide and penicillin.

The difference in fatality rates between the two groups of cases in relation to the age of the patient were as follows:-

In patients aged six months and under, 10 per cent higher in Group A than in Group B.

In patients aged from six months to one year, 51 per cent higher in Group A than in Group B.

In patients aged from two to three years, 33.3 per cent higher in Group A than in Group B.

In patients aged from three to four years, 33.3 per cent higher in Group A than Group B.

THE/

THE DURATION OF THE ILLNESS BEFORE THERAPY WAS COMMENCED AND ITS INFLUENCE ON THE FATALITY RATE.

It would be expected that the longer a patient is ill before a proved form of therapy is instituted the firmer hold the disease would obtain and the more difficult it would be to cure. The distribution of the cases in the two groups A and B with regard to the day of illness before therapy was instituted and their corresponding fatality rates are shown in Table No.13 set forth below.

TABLE NO. 13.

THE DISTRIBUTION OF THE CASES IN THE VARIOUS DAYS OF ILLNESS BEFORE THERAPY WAS COMMENCED WITH FATALITY RATES.

Duration of Illness Before Treatment.	Group A.		Group B.	
	No. of cases.	No. of Deaths.	No. of Cases.	No. of Deaths.
1 Day.	6	5 (83)	6	1 (16.6)
2 Days.	18	5(27.7)	27	3 (11.1)
3 Days.	16	4 (25)	9	1 (11.1)
4 Days.	3	0 (-)	3	0 (-)
5 Days.	3	0 (-)	0	0 (-)
5 - 10.	4	2 (50)	5	2 (40)
Total.	50	16 (32)	50	7 (14)

(Figures in brackets are percentages).

It will be noted that in Group A the highest fatality rate occurred in the cases admitted in their first day of illness: 83 per cent. It then dropped to zero in the fourth and fifth days but/

but rose sharply again in the fifth to tenth day to 50 per cent. In Group B the fatality rate was high in those cases admitted in their first day of illness, being 16.6 per cent, dropping from 11.1 per cent on the second and third days to zero in the fourth and fifth days of illness, rising again during the fifth to tenth day to 40 per cent. It was surprising that the fatality rate should have been so high for cases in which treatment was instituted at an early stage, and it was decided to investigate the type of patient with regard to age, admitted within the first two days of illness. Tables Nos. 14 and 15 illustrate the distribution of the cases with regard to age admitted in the first and second days of illness respectively.

TABLE NO. 14.

DISTRIBUTION OF CASES IN THEIR VARIOUS AGE GROUPS, WHICH WERE ADMITTED IN THE FIRST DAY OF ILLNESS.

Age of Patient.	Group A. No. of Cases.	Group A. No. of Deaths.	Group B. No. of Cases.	Group B. No. of Deaths.
1 Year & Under.	3	3(100)	5	1(20)
2 Years & Under.	2	1(50)	1	-(-)
3 Years.	1	1(100)	-	-(-)
4 Years.	-		-	
5 Years.	-		-	
Total.	6	5(83.3)	6	1(16.6)

(Figures in brackets are percentages).

TABLE NO. 15.

DISTRIBUTION OF CASES IN THE VARIOUS AGE GROUPS, WHICH WERE ADMITTED IN THE SECOND DAY OF ILLNESS.

Age of Patient.	Group A.		Group B.	
	No. of Cases.	No. of Deaths.	No. of Cases.	No. of Deaths.
1 Year & Under.	6	4(66.6)	9	2(22.2)
2 Years & Under.	4	-	8	-
3 Years.	3	-	5	-
4 Years.	3	1(33.3)	2	-
5 Years.	2		3	-
Total.	18	5(27.7)	27	2(7.4)

(Figures in brackets are percentages).

The 6 cases in Group A which were admitted in their first day of illness were three years of age and under, and five of them died giving a fatality rate of 83.3 per cent. In Group B there were 6 cases and all were under two years of age. In fact, five of the patients were infants of one year of age and under, and it was in this group that the only death occurred. Thus the great majority of cases admitted in their first day of illness were infants of one year of age and under, the percentage for Group A was 50 and Group B 83.3. The difference in the fatality rates was remarkable considering the fact that there were a greater number of infants of one year of age and under in Group B,/

B, in which the fatality rate was lowest being 20 per cent, as compared with 100 per cent in Group A. From Table No. 15 it will be seen that there was a more even distribution of the cases in the second day of illness over all the age groups, but the incidence of the disease was still highest in children up to two years of age.

Again there is a marked difference in the fatality rates which are higher in the cases treated by penicillin alone, than in the penicillin and sulphonamide treated group. For example six children of one year of age and under were treated in Group A, with a fatality rate of 66.6 per cent, as compared with a fatality rate of 22.2 per cent in Group B.

The results obtained from the use of penicillin and sulphonamide were infinitely better, regardless of the duration of illness before treatment was instituted, than that obtained from the use of intrathecal penicillin alone.

GROUP "A".

TABLE XVI: TOTAL CELL COUNT.

No. of Cells per cmm.	DAYS OF ILLNESS.									
	1	3	5	7	9	11	13	15	17	19
1000+	48	36	10	2	1	~	~	~	~	~
750~1000	~	4	13	5	2	1	~	~	1	~
450~750	~	1	13	9	5	3	~	~	~	~
150~450	2	2	6	19	18	7	6	3	2	1
0~150	~	~	~	6	8	13	4	3	~	~
No. of Convalescent cases	~	~	~	~	6	14	27	31	34	34
Total no. of Deaths.	~	7	8	9	10	12	13	13	13	15*
Total	50	50	50	50	50	50	50	50	50	50

TABLE XVII:- DIFFERENTIAL CELL COUNT.

Polymorphs per. cent.	DAYS OF ILLNESS.									
	1	3	5	7	9	11	13	15	17	19
80~90	48	26	11	3	2	1	~	~	~	~
70~80	1	11	6	4	3	~	~	~	~	~
60~70	1	6	19	7	3	3	1	~	~	~
50~60	~	~	1	4	2	~	~	~	~	~
40~50	~	~	2	12	10	5	2	1	1	1
30~40	~	~	3	6	7	2	1	2	2	~
-30	~	~	~	5	7	13	6	3	~	~
No. of Convalescent Cases	~	~	~	~	6	14	27	31	34	34
Total no. of Deaths	~	7	8	9	10	12	13	13	13	15*
Total	50	50	50	50	50	50	50	50	50	50

*One other patient died on the 64th day.

GROUP "B".

TABLE XVIII: TOTAL CELL COUNT.

No. of Cells per cmm.	DAYS OF ILLNESS.							
	1	3	5	7	9	11	13	15
1000+	50	31	4	~	~	~	~	~
750~1000	~	8	2	~	~	~	~	~
450~750	~	5	19	4	2	~	~	~
150~450	~	1	19	23	5	1	~	~
0~150	~	~	~	16	20	6	1	~
No. of Convalescent Cases	~	~	~	~	16	36	42	43
Total no of Deaths.	~	5	6	7	7	7	7	7
Total	50	50	50	50	50	50	50	50

TABLE XIX: DIFFERENTIAL CELL COUNT.

Polymorphs per. cent	DAYS OF LLLNESS.							
	1	3	5	7	9	11	13	15
80~90	50	26	5	1	1	~	~	~
70~80	~	14	6	3	~	~	~	~
60~70	~	4	12	4	3	1	~	~
50~60	~	1	7	~	~	~	~	~
40~50	~	~	9	10	2	~	~	~
30~40	~	~	5	13	3	2	~	~
-30	~	~	~	12	18	4	1	~
No. of Convalescent Cases	~	~	~	~	16	36	42	43
Total No. of Deaths.	~	5	6	7	7	7	7	7
Total	50	50	50	50	50	50	50	50

THE TOTAL AND DIFFERENTIAL CELL COUNT AS AN INDICATION OF THE RATE OF RESOLUTION OF THE DISEASE PROCESS.

As explained in an earlier chapter a total and differential cell count on the cerebrospinal fluid was performed after each lumbar puncture, the results have been tabulated in tables, 16, 17, 18, 19 on the opposite page. It was noted that practically all cases in both groups had on admission a turbid fluid with a cell count of 1000 plus cells per c.m.m. As the condition improved, however, the total cell count steadily dropped and the proportion of polymorphonuclear leucocytes, which at first formed over 80 per cent of the total cells, followed a parallel course being replaced by lymphocytes.

In Group A, at the initial lumbar puncture, the cerebrospinal fluid in 48 cases was turbid and had a total cell count of 1000 plus cells per c.m.m. The two remaining cases in Group A had cell counts of 220 and 320 cells per c.m.m. respectively. Both these cases were found subsequently to have developed hydrocephalus.

On the third day of hospital treatment the cell counts were again high, this being particularly true of the Group A cases, which had received an intrathecal dose of 50,000 units of penicillin. There were 36 cases in Group A with fluids which had a total cell count of 1000 plus cells per c.m.m. Four cases had total cell counts ranging between 750 to 1000 cells per c.m.m; two of the cases in this group were at a later date found to have developed hydrocephalus, and the other two had low cell counts on admission of 1,200 and 1,420 cells per c.m.m. respectively. One case had a cell count of 422 cells per c.m.m. and she was also found at a later date to have developed hydrocephalus. There were two cases which had particularly low cell counts on the third day of treatment. One/

One of them had a low cell count on admission, and, as already explained, hydrocephalus had developed. The other case was moderately ill on admission and had a total cell count of 1000 plus cells per c.m.m. There was a marked decrease in the total cell count on subsequent days and the pressure was slightly reduced. The patient was very lethargic, and the question of hydrocephalus having developed was considered. However, no definite evidence was obtained, the patient made a good recovery, and was discharged on the 92nd day in hospital, after a long convalescence.

On the fifth day of treatment in Group A the total cell counts were still high. In 10 cases total cell counts of 1000 plus cells per c.m.m. were recorded and in the remainder they varied from 150 to 1000 cells per c.m.m.

It was not until the seventh day of treatment in hospital that the cerebrospinal fluid showed a marked inprovement. Until then, the patients had distinctly opalescent fluids, but at this stage in six cases the cerebrospinal fluids had total cell counts of below 150 cells per c.m.m. and appeared clear. From this date onwards the number which had clear fluids gradually increased, and by the 17th day all the cases which recovered had clear fluids.

In Group B all the cases had turbid fluids on admission with total cell counts of 1000 plus cells per c.m.m. By the third day of treatment, 31 cases had again total cell counts of 1000 plus cells per c.m.m., 8 had counts ranging between 750 and 1000 cells per c.m.m., 5 had counts of between 450 and 750 cells/

cells per c.m.m., and one case had a total cell count of 400 cells per c.m.m. All the cases which demonstrated such low cell counts on the third day of treatment were moderately ill, and their fluid at the initial lumbar puncture was not so turbid as those of the other cases.

By the ninth day of treatment in hospital there were 20 cases whose cerebro-spinal fluids had total cell counts of below 150 cells per c.m.m., and appeared clear. All the cases had cell counts below 150 cells per c.m.m., by the fifteenth day of treatment. With regard to the differential cell counts of the cerebrospinal fluid it was found that the cells were, at first, mainly polymorphonuclear but as the condition of the patient improved, they gradually decreased in number and were replaced by lymphocytes. By the 11th day in Group A and the 9th day in Group B the cells were mainly lymphocytes.

On comparing the two groups of cases A and B it was found that the total and differential cell counts showed evidence of improvement at a much earlier stage in Group B cases than in Group A. For example it was not until the 17th day in Group A that all the cases which recovered had total cell counts below 150 cells per c.m.m. Whereas in Group B this was attained by the 15th day. In Group B, 36 out of 43 cases which recovered had clear fluids by the 11th day, and in Group A it was not until the 15th day that a similar result was obtained, when 31 out of the 34 cases had clear fluids.

THE DURATION OF PYREXIA.

The temperature as already observed was no criterion of severity and tended to follow a very irregular course. While the disease process was active it was unsettled and was generally elevated but as the infection was arrested and the inflammatory process subsided it tended to assume a more normal course. The duration of pyrexia in the cases which recovered in both groups are shown below in Table No. 20.

TABLE NO. 20.

DURATION OF PRIMARY PYREXIA IN BOTH GROUPS.

Duration of Primary Pyrexia in days.													
	1	2	3	4	5	6	7	8	9	10	11	12	13
No. of Cases Group A.			1			14	4	5	4	2	1	1	2
No. of Cases Group B.	1	3	4	11	11	4	8	0			1		

The duration of pyrexia in Group A ranged from three to thirteen days, and in Group B from one to eleven days. By the end of the seventh day of treatment the temperature had settled in 19 cases out of the 34 cured (55.8 per cent) in Group A and in Group B in 42 out of the 43 cases (97.6 per cent). It was not until the tenth day of treatment that a similar number in Group A (88.2 per cent) had normal temperatures. Following the return to normal of the temperature, and the cerebrospinal fluid/

fluid, and the disappearance of the other signs and symptoms of the disease, the patients were kept in hospital for at least a further fourteen days, this depended on their progress and general health in convalescence.

COMPLICATIONS OCCURRING IN BOTH GROUPS OF CASES.

The complications and sequelae which occurred were classified into two main groups; those which were directly attributable to the meningitis such as strabismus and hydrocephalus, and those due to other infections such as enteritis and pneumonia.

Their distribution in Groups A and B are shown in the accompanying Tables No. 21 and 22.

TABLE NO. 21.

DISTRIBUTION OF CASES IN THE TWO GROUPS DEVELOPING STRABISMUS OR HYDROCEPHALUS.

Group.	Hydrocephalus.	Strabismus.
A.	5	0
B.	0	2

TABLE NO. 22.

DISTRIBUTION OF CASES IN GROUPS A AND B DEVELOPING ENTERITIS OR PNEUMONIA.

Group.	Gastro-Enteritis.	Pneumonia.
A.	5	0
B.	1	1

Internal/

Internal hydrocephalus was the only sequela of the meningitis. It occurred in 5 cases in Group A, and all proved fatal. There were no cases in Group B which developed hydrocephalus. The 10 per cent incidence of this sequela is higher than that of the Scottish Scientific Advisory Committee (1944) who reported 2 per cent for serum treated patients and for sulphonamide treated between 2 and 3 per cent.

Internal hydrocephalus is usually associated with cases which have become subacute, but it does occur at a comparatively early stage. (Worster-Drought and Kennedy 1919). In fact Gordon (quoted from Briton 1941) reports that it occurred in some of his cases as early as the 8th day of illness, however, Brinton (1941) pointed out that it is not the cause of symptoms until the acute phase is subsiding. Its clinical onset is occasionally abrupt, but much more frequently insidious. Headache accompanied by vomiting begins early and increases to an intolerable severity. Progressive dementia follows and the body slowly wastes till little more than skin and bones remain. In infants there is visible enlargement of the head, due to separation of the cranial sutures.

The signs and symptoms of hydrocephalus developed in two cases who survived to the 67th and 25th day of illness, respectively. No signs of symptoms developed in the others who died in their 5th, 13th and 14th/

14th days of illness respectively, a definite diagnosis of hydrocephalus was established at autopsy. The patient who died in his fifth day of illness was aged 3 years, and was reputed to be in his 4th day of illness on admission. He was severely ill and had marked retraction. At autopsy he was found to have basal adhesions, with pus covering the whole of the brain, and the lateral ventricles were distended with fluid. The findings at autopsy, together with his condition on admission, suggested that the illness had been of longer duration.

The distribution of the cases with regard to age, duration of illness before being admitted to hospital, and duration of treatment in hospital before death occurred, are shown in the accompanying Table No. 23.

TABLE NO. 23.

DISTRIBUTION OF CASES DEVELOPING HYDROCEPHALUS.

Case.	Age.	Duration of Illness on Admission.	Duration of Illness in Hospital before Death.
1 E.B.	6 Weeks.	5 Days.	8 Days.
2 M.G.	11 "	6 "	19 "
3 D.H.	8 Months.	2 "	12 "
4 C.Mc.	3 Years.	4 "	1 Day.
5 E.S.	4 "	3 "	64 Days.

It was remarkable that hydrocephalus did not appear in any/

any of the cases treated with sulphonamide and penicillin. This may be due to the fact that the disease in the penicillin treated group ran a longer course, and thus the risk of passing into a sub-acute stage was greater.

STRABISMUS.

In Group A none of the patients developed strabismus, while in Group B it appeared in two cases in their fourth and eighth day of illness respectively. The condition cleared up before the patient was discharged. Strabismus generally appears in the acute stage of the illness, and occurs as a result of injury to the 6th nerve, which is more liable to be affected because of its long intracranial course.

In Table No. 24 below, the cases which developed strabismus are set forth, with the time of onset, and the duration of stay in hospital.

TABLE NO. 24.

CASES WHICH DEVELOPED STRABISMUS.

Case	Age.	Day of Illness On Admission.	Day of Development after Admission.	Result of Treatment.	Duration of Stay in Hospital.
J.N.	4/12	6	2	Cured.	50 Days.
M.T.	10/12	1	3	Cured.	45 Days.

ENTERITIS.

This complication developed in 5 cases in Group A, and

in/

in one case in Group B. Tables No. 25 and 26 show the distribution of the cases in both groups.

CASES DEVELOPING GASTRO-ENTERITIS, SHOWING DAY OF ILLNESS BEFORE ADMISSION TO HOSPITAL, THE DATE OF ONSET, AND THE RESULT OF TREATMENT.

TABLE NO. 25.

Group A.

Case.	Age.	Duration of Illness before Admission.	Date of Onset In Hosp.	Result.	Days Ill in Hosp. Before Death.
1 B.K.	6/12	3 Days.	2nd Day.	Died.	11 Days.
2 D.Mc.	7/12	1 Day.	8th "	Died.	11 "
3 L.Mc.	9/12	3 Days.	5th "	Died.	5 "
4 J.Mc.	6/12	1 Day.	7th "	Died.	19 "
5 J.C.	6/12	2 Days.	9th "	Cured.	

TABLE NO. 26.

DISTRIBUTION OF CASES DEVELOPING ENTERITIS IN GROUP B.

Group B.

Case.	Age.	Duration of Illness before Admission.	Date of Onset in Hosp.	Result.	Days Ill in Hosp. Before Death.
A.B.	13/12	3 Days.	28th Day.	Cured.	-

Of the 5 cases in Group A which developed enteritis, four proved fatal. In the case which survived, the infection did/

did not develop until the 11th day of illness and it was not severe and responded well to sulphaguanadine. The only case in Group B which contracted enteritis recovered, the condition having made its appearance on the 28th day of illness in hospital, during the convalescent stage of the meningitis, and it responded well to sulphaguanadine and intraperitoneal salines.

The duration of illness before enteritis made its appearance in Group A averaged 6 days. By the 6th day of illness the resistance of the infant was sufficiently lowered to permit the activation of intestinal organisms which are normally nonpathogenic, and thus increased the susceptibility to bowel infection. The prevalence of enteritis at the time the cases were treated is of interest. In Group A one case was admitted to hospital in August, two cases in September, one in October, and one in November. On consulting the hospital records it was found that the number of admissions of cases with enteritis in the period August to November averaged approximately 24 per month and over the first five months of 1946, averaged approximately 6 per month. Enteritis was certainly more prevalent at the time when Group A cases were admitted, but all the cases developed the disease on an average 6 days after admission to the ward and there was no evidence of contact in any form being made with other patients having the disease.

It is felt that the longer duration of illness with a corresponding/

corresponding lowering of resistance in the patients who were treated by penicillin was a definite factor in predisposing to the infection. In addition the sulphonamides administered to the other group of patients would have an inhibiting effect on some organisms, which might cause or predispose to the disease.

Only one case, which was in Group B, developed pneumonia.

He was aged 18/12 and was admitted in his second day of illness with a history of vomiting and convulsions. The respirations were rapid and fine crepitations were heard throughout both lungs. He died six hours later.

At autopsy there was evidence of pneumonia with basal adhesions in the left lung.

CONCLUSIONS.

In every factor considered, penicillin used in combination with sulphonamide produced the better results. The fatality rate in Group B cases was less by 18 per cent than in Group A. The duration of the primary pyrexia was shorter by at least three days, and the cerebrospinal fluids in the penicillin and sulphonamide treated cases returned to normal much quicker. The majority of cases in Group B had clear fluids by the eleventh day, whereas in Group A this was not attained by a similar number until the fifteenth day.

The incidence of sequelae and complications such as hydrocephalus and enteritis were higher by 10 and 8 per cent respectively in the cases which were treated by intrathecal penicillin alone. Hydrocephalus was noted to occur in 10 per cent of cases in Group A, and its high incidence was attributed to the failure of the penicillin to counteract the disease in its early stages, with the result that it became subacute.

Enteritis was more prevalent when the cases in Group A were admitted, but the cases which developed this complication did not do so until, on an average, the sixth day in hospital. There was little doubt that the prolongation of the acute stage of the illness, with a corresponding weakening of the patient's power of resistance, predisposed to the infection. In addition, the sulphonamide administered to the Group B cases, would have an inhibiting effect on some organisms which might cause enteritis.

The/

The disease was noted to have manifested features which were of graver prognostic significance, in a few more cases in Group A, than in Group B. However, the difference obtained in the results between the two groups was so great that these factors could have played but a small part. There was little doubt that the chief cause of the improvement in the results in Group B cases was the form of therapy employed. The combination of sulphonamide with penicillin was undoubtedly the better form of treatment.

CHAPTER V.

FREQUENCY DISTRIBUTION OF BACTERIOSTATIC TITRES OF PENICILLIN IN THE CEREBROSPINAL FLUID.

TABLE XXVII: GROUP "A" [27 cases]

Bacteriostatic Titre. [Florey's Staphylococcus]	Days in hospital when estimated.						
	1	3	5	7	9	11	13
No Inhibition	21	18	8	2	1	1	1
Neat Serum	6	8	17	21	19	9	3
1/2 dilution	~	1	2	4	2	4	1
1/4 dilution.	~	~	~	~	1	2	~
1/8 dilution.	~	~	~	~	~	~	~
1/16 dilution	~	~	~	~	~	~	~
Total no. of cases	27	27	27	27	23※	16※	5※

TABLE XXVIII: GROUP "B" [34 cases]

Bacteriostatic Titre [Florey's Staphylococcus]	Days in hospital when estimated.				
	1	3	5	7	9
No Inhibition.	25	21	13	9	5
Neat Serum.	9	12	18	22	13
1/2 dilution.	~	1	3	3	2
1/4 dilution.	~	~	~	~	~
1/8 dilution.	~	~	~	~	~
1/16 dilution.	~	~	~	~	~
Total no. of cases	34	34	34	34	20※

※At this stage certain patients were convalescent and titres were not estimated.

BACTERIOSTATIC TITRE RESULTS.

After each lumbar puncture the bacteriostatic titre was determined, and thus an estimate of the concentration of penicillin remaining in the cerebrospinal fluid 48 hours after its intrathecal administration was obtained. Although there were 50 patients in each group it was only in 27 cases in Group A, and 34 in Group B that serial bacteriostatic titres were recorded. The inability to estimate serial titres in the other cases was influenced by many factors such as the death of the patient, contaminations etc. The results have been recorded in the Tables No. 27 and 28 shown on the opposite page.

There were 6 cases in Group A and 9 cases in Group B, whose cerebrospinal fluid on admission, before the administration of penicillin, inhibited the growth of a standard Florey staphylococcus in neat solution. On the third day inhibition of growth occurred at a higher dilution in only 4 cases in Group A, and in 5 cases in Group B. This was surprising, considering the fact that 50,000 units of penicillin in Group A and 30,000 units in Group B were injected intrathecally 48 hours earlier. The rise in titre in one case in Group A was from inhibition in neat fluid recorded at the first estimation to inhibition of growth in a dilution of $\frac{1}{2}$. The rise in titre in the remaining 3 cases was from no inhibition to inhibition in neat fluid. In Group B similar results were recorded. One case showed a rise in titre from neat fluid to a dilution of $\frac{1}{2}$, and/

and the remaining 4 cases from no inhibition to inhibition in neat fluid.

From the fifth day onwards inhibition of growth occurred in higher dilutions showing that the concentration of penicillin in the cerebrospinal fluid was increasing. This was particularly true of the cases in Group A, for by the 7th day inhibition of growth of the Florey staphylococcus was produced in the fluid of 4 cases in a dilution of $\frac{1}{2}$, of 21 cases in neat fluid, and in only 2 cases was the concentration of penicillin in the fluid insufficient to prevent growth. The highest dilution recorded in Group A which inhibited the growth of the Florey staphylococcus was $\frac{1}{4}$, and this level was not reached until the 9th day. In Group B the titres did not rise to the same extent, the highest dilution at which growth was inhibited was $\frac{1}{2}$, and there were several cases whose fluid even when convalescence was approached did not contain a detectable quantity of penicillin.

From the results it appeared that the rate of excretion of the penicillin was more rapid over the first seven days of treatment. As the patient approached convalescence, the excretion from the cerebrospinal fluid was less rapid, and a quantity of penicillin sufficient to inhibit growth of the Florey staphylococcus in higher dilutions remained.

Rammelkamp & Keefer (1943) have shown, that the rate of excretion of intrathecal penicillin in cases of meningitis is/

is much more rapid than in normal individuals, but following the intrathecal injection of 10,000 units demonstrable quantities were present up until 24 hours after injection.

This more rapid excretion of penicillin in meningitis is due to the impairment of the blood-cerebrospinal fluid barrier. The results obtained in both series of cases show that as the inflammation in the meninges subsided the "barrier" became more effective and the penicillin concentration in the fluid rose.

It has been shown by Fleming and Young (1944), that the greater the dose of penicillin administered the longer it takes to be excreted.

In Group A cases after the 7th day, the penicillin was present 48 hours later in greater concentration in the cerebrospinal fluid, than in Group B cases. The explanation being that Group A cases received an intrathecal dose of 50,000 units, as compared with 30,000 units in Group B.

CONCLUSIONS.

In the first few days of illness when the patient is acutely ill, an adequate concentration of the penicillin is desirable in order to control the infection. The dose of penicillin administered in both groups of cases A and B, was inadequate in the first few days of illness to provide this concentration for 48 hours in the cerebro-spinal fluid. To obtain a more constant level, the intrathecal injection of penicillin would require to have been made at more frequent intervals, and if so an adequate bacteriostatic level could have been obtained by using a smaller dose.

CHAPTER VI.

THE TOXIC EFFECTS OF PENICILLIN ON THE CENTRAL NERVOUS SYSTEM.

The toxicity of penicillin applied locally or systemically by intravenous, intramuscular, or subcutaneous means is slight. The toxic reactions which occur were noted to be proportional to the purity of the salt used. The tissues of the central nervous system are, however, particularly sensitive, and it was found that a penicillin salt which on the other tissues caused no reaction, shows evidence of toxicity when applied to them. For example Rammelkamp and Keefer (1943) observed that, following an intrathecal injection of 10,000 Florey units of penicillin in a normal subject, headache and vomiting occurred, and there was an increase in the intrathecal pressure with phagocytosis in the spinal fluid.

Rosenberg and Arling (1944) reported, following the treatment of their large series of cases of meningococcal meningitis with intrathecal and systemic penicillin that, in those patients who received penicillin intrathecally every 12 hours, as well as in individuals who were given intrathecal doses of 15,000 units, headache was more severe and persistent, the fever was more prolonged and the signs of meningitis subsided more slowly. They noted that the penicillin produced by different manufacturers caused varying degrees of meningeal irritation.

Johnson and Walker (1945) drew attention to the danger

of/

of administering a high dose of penicillin intrathecally. They treated a patient with a staphylococcal infection of the ventricular system with an intraventricular injection of 50,000 Oxford units. Within an hour the patient was comatose, and in vascular collapse. Supportive therapy improved the condition but the patient had clonic spasms of the arms, legs and neck, for several hours. Within a day the patient appeared normal. Two days later an intraventricular dose of 15,000 units produced a similar but less severe reaction. They were convinced that the intraventricular injection of the drug was the cause of the reaction and recommended that intraventricular penicillin be used in small amounts.

Cairns and his colleagues (1944) reported, that with sodium or calcium penicillin salts containing 250 to 500 units per m.g.m, a mild reaction was observed immediately after intraventricular injection. It consisted of a patchy erythema of the skin of the trunk and limbs, often coming and going, generalised sweating, intermittent goose skin, slight rise of pulse rate and sometimes vomiting, the whole passing off in 10-20 minutes. The dose which they administered was from 2,000 to 4,000 units daily. In addition they noted that following injection by lumbar puncture the patient often complained of pain in the sacral region, spreading down the sciatic distribution and lasting up to a minute. Further in one case where a solution of penicillin containing only 97 units/

units per milligramme was injected into the lateral ventricle, the patient developed a severe reaction with evidence of brain stem involvment. They found that a preparation of 300 units per mgm. of penicillin produced in 3 subjects with normal meninges symptoms of meningitis which subsided in 48 hours. The dose injected was 40,000 units. When they used a purer preparation of 500 units per mgm., there were no toxic reactions.

Sweet and his colleagues (1945), following the daily administration of from 20,000 to 40,000 units of penicillin intrathecally, had 4 cases developing neurological reactions. They were of two types, mild sensory changes and severe sensory and motor changes. Both types of lesions involved the lower segments of the spinal cord, or the roots of the lumbo-sacral plexus of nerves. The mild sensory changes consisted of pains in the legs and back, and first appeared on the 10th and 23rd days after the institution of intrathecal penicillin therapy, and they persisted until the penicillin dosage was reduced or discontinued.

The severe reactions occurred in patients who had prolonged intrathecal penicillin and consisted of severe pain in the legs and toes which first appeared on the 10th day of treatment. By the 17th day there was urinary retention with overflow, and the presence of a hypotonic bladder was verified by cystometrogram. In due course, in addition to the above symptoms, there was paralysis of both legs, with pronounced hyperaesthesia/

hyperaesthesia and absent tendon reflexes. In all cases there was complete recovery of function before the patients were discharged from hospital.

Experimentally in animals Russell and Beck (1945) have shown that a concentrated solution of sodium penicillin had an irritant effect when applied to the brain surface. In one case there was massive necrosis of the cortex.

As already stated the cases in Group A were given on admission and on alternate days thereafter an intrathecal dose of 50,000 units of penicillin which contained from 300 to 500 units per mgm. The dose was administered by lumbar puncture in 5 c.c. of sterile water. Toxic reactions were noted following the administration of the intrathecal penicillin, and these could be divided into two main types. Those which occurred immediately after the injection of the penicillin, and consisted of pain in the lumbro-sacral region, which tended to radiate down one or both legs along the distribution of the sciatic nerve. This pain was severe, being at its maximum intensity at the moment of onset, and then gradually passed off over the next five minutes.

The second type of reaction experienced was convulsions. They occurred in the majority of cases about one hour after the penicillin was administered intrathecally by the lumbar route. Usually there were prodromal manifestations which first made their appearance about 15 minutes after the drug was given. The course/

course of events was as follows:- The patient's face which was at first flushed became very pale, and the pupils gradually dilated. The pulse became very rapid and thready, and was barely palpable. Older children complained of feeling cold and rigors were frequent. On an average one hour after the intrathecal injection, paroxysmal, generalised clonic spasms of the arms, legs and neck occurred, and while these were in progress cyanosis was marked. An attack generally lasted from two to five minutes, and its termination was frequently followed by slight vomiting. In cases which had a severe reaction the convulsions recurred at short intervals for about $1\frac{1}{2}$ hours. In the milder cases the attacks were not so severe, and the interval between them was longer, the seizures consisting of slight twitchings of the arms and legs.

After the stage of convulsions, the child's condition gradually improved, the pulse rate slowed down, and its volume increased. The pupils and colour returned slowly to normal. The stuporose state which followed the convulsions passed off and in about 5 hours the child was as mentally alert as he was before the administration of the drug.

There were no residual sequelae in the form of paralysis or sensory loss in any of the cases following the toxic reactions described above.

The toxic manifestations did not occur after every intrathecal/

intrathecal administration of the penicillin, and they did not appear to be related to the degree of illness of the patient.

An autopsy was performed in 4 cases which had convulsions after intrathecal penicillin. In three of these the post mortem examination was carried out within 24 hours of the patient being admitted to hospital and of the administration of the first dose of intrathecal penicillin which the convulsions followed. In the other case, the autopsy was performed on the 8th day, after an attack of convulsions which followed the intrathecal administration of the penicillin on the first day in hospital. In all 4 cases, pus covered the surface and base of the brain. Two cases showed evidence of hydrocephalus, with basal adhesions and dilatation of the lateral ventricles. There was no evidence of injury to the meninges or the brain, other than that usually associated with meningococcal meningitis, which might have accounted for the toxic manifestations.

With regard to treatment, the lumbro-sacral pain passed off in about five minutes and nothing was done for it. In the cases which developed convulsions, treatment was instituted immediately any evidence of a toxic reaction was noted. In the early stages the patient was kept warm with hot water bottles and a shock cradle. Syrup of chloral was administered in a dose of 30 minims for infants up to one year of age, and in older children one drachm was given. This was successful in controlling the/

Table XXIX :- CASES HAVING TOXIC REACTION TO PENICILLIN IN GROUP "A".

AGE.	TOXIC REACTION		Severity of attack of convulsions	No. of attacks.	Dose of intrathecal penicillin which they followed.	Time of Onset after Injection		Duration of :-		Total duration of reaction	Duration of illness before convalescence was reached.
	Lumbo-sacral Pain	Convulsions				Lumbo-sacral Pain	Convulsions	Lumbo-sacral Pain	Convulsions		
6 weeks		+	Fairly Severe	1	1st.		1hr		1 hr.	5hrs.	Died 8th day
4 months		+	Slight.	2	3rd.		2hrs		¾ hr.	4hrs.	15 days
					4th.		1hr.		1 hr.	5 hrs.	
5 months		+	Slight.	1	1st.		1hr.		1hr.	6hrs.	7days.
6 months		+	Slight.	1	2nd.		1hr.		¾hr.	6hrs.	Died of Enteritis 11th day
6 months		+	Slight.	1	5th.		1hr.		1hr.	6hrs.	15 days.
6 months		+	Slight.	1	2nd.		1hr.		1hr.	7hrs.	15 days.
7 months		+	1 Slight. 2 Severe.	3	3rd		1hr.		1hr.	4hrs	Died 11th day
					4th		1hr.		1½ hrs.	8hrs	
					5th.		3hrs		1½ hrs.	8hrs	
7 months		+	Severe	1	1st.		3hrs.		1½hrs.		Died within 24 hrs. of admission.
13 months		+	Slight.	1	1st.		¾hr.		1hr.		Died within 24hrs. of admission
13 months	+	+	Slight.	1	2nd.	Immediate.	1hr.	5 mins.	1hr.	4hrs.	11 days.
14 months		+	Slight.	1	2nd.		1hr.		¾hr.	3hrs.	7days.
15 months	+	+	Slight.	1	1st	Immediate	2hrs.	5 mins.	¾hr.	4hrs.	11 days
15 months		+	Slight	1	4th		1hr.		2hrs.	5hrs.	11 days
20 months		+	Slight.	1	2nd		1hr.		¾ hr.	3hrs.	7 days
20 months	+	+	Slight.	1	1st	Immediate	1hr.	5 mins.	1hr.	6 hrs.	7 days
21 months	+	+	Slight.	1	2nd.	Immediate	2 hrs.	5 mins.	1hr.	4 hrs.	11 days
2 years		+	Severe.	1	1st.		1hr.		1½ hrs.	6 hrs.	11 days
2½ years	+	+	Slight.	1	2nd.	Immediate	½ hr.	5 mins.	1hr.	5 hrs.	9 days
3 years.		+	Slight.	1	1st.		1hr		1hr.		Died within 24hrs. of admission.
3 years.		+	Slight.	1	1st.		1hr.		¾hr.	5hrs.	Died 7th day
4 years.	+			1	3rd.						13 days
4 years.	+			1	2nd.						9 days

the mild toxic reactions, but in cases which reacted severely more energetic treatment was necessary. In an endeavour to control the convulsions in a severe case, lumbar puncture was performed and the subarachnoid space drained. In addition 1½ grains of sodium phenobarbitone were given intramuscularly. In one case these measures were unsuccessful and to control the convulsions a chloroform anaesthetic was administered.

In Table No. 29, on the opposite page, the cases are listed according to age, number and type of reaction, the time of onset after administration of the drug, the duration of the attack, and the length of time the patient was ill before death or convalescence occurred.

It will be noted that out of 22 cases in only 2 patients was lumbosacral pain by itself the only indication of a toxic reaction. In 5 patients lumbo-sacral pain was experienced in addition to convulsions. The toxic reaction to the intrathecal penicillin in the other 15 cases was confined entirely to convulsions. Three cases had severe attacks of convulsions, but in all the others the attacks were slight. The reactions occurred after only one dose in 20 of the cases, of which nine were after the first dose, eight after the second and one after the third, fourth and fifth doses respectively. The remaining two cases had more than one attack. In one of them, aged 4 months, convulsions followed the third and fourth intrathecal dose of penicillin.

The/

The course of the illness in this case was prolonged, convalescence not being reached until the 15th day. In the other case convulsions occurred as a toxic manifestation following the intrathecal administration of the drug in the third, fourth and fifth doses. The first attack was slight but on the other two occasions severe. The patient died of gastro-enteritis on the 11th day of illness.

The sodium penicillin salt which was used contained from 300 to 500 units per mgm., and was manufactured by Messrs. Boots, and Glaxo Laboratories. The toxic reactions experienced were probably due to the impurities in the salt and also to the high dosage administered intrathecally. A dose of 50,000 units caused the toxic reactions related in Group A cases, but in Group B cases where only 30,000 units were administered there were no reactions. The penicillin salts although of the required therapeutic standard of purity vary in toxicity with the different manufacturers, but in this series of cases the reaction could not be attributed to any one particular brand. It is interesting to note that Johnson and Walker (1945) attributed the convulsions in their case not only to over-dosage, but to an idiosyncrasy to the drug. They point out that electroencephalograms of many patients receiving penicillin are distinctly abnormal.

CONCLUSIONS.

Toxic reactions followed the intrathecal administration of penicillin in 22 cases. In 15 cases convulsions occurred as the only toxic reaction and of these 77.2 per cent were patients aged 2 years or under. Lumbo-sacral pain was complained of by 7 cases and of these 5 later developed convulsions. In the remaining 2 cases there was no further evidence of a toxic reaction other than the lumbo-sacral pain. The attacks generally began one hour after the penicillin was administered and recurred at intervals for about one hour. In six hours on an average the patient had completely recovered. The lumbo-sacral pain on the other hand was at its maximum intensity immediately after the injection and then passed off over the next five minutes. These toxic reactions were undoubtedly caused, chiefly, by the impurities in the penicillin salts which consist mainly of pyrogenes. The lumbo-sacral pain resulting from irritation of the cauda equina and the convulsions by irritation of the cerebral cortex and higher centres. The younger children appeared to be particularly susceptible to the impurities in the salt, and the reaction, in the majority of cases followed the first or second intrathecal dose of the drug.

CHAPTER VII.

THE INVESTIGATION OF THE QUANTITATIVE AND QUALITATIVE CHANGES IN THE BLOOD IN CEREBROSPINAL FEVER.

It was originally intended to estimate the bacteriostatic titre of the blood every 48 hours, before lumbar puncture was performed, and thus obtain a reading for the concentration of penicillin in the blood, and compare it with titres found in the cerebrospinal fluid. It was, however, difficult to get a specimen of blood in every case, and it was thought inadvisable to enter repeatedly the saggital sinus, as was done for the blood culture specimen on admission. As an alternative, it was decided to study the variations which occur in the white cells in meningitis.

The total and differential cell counts were estimated twice during the first week and once a week for the remaining three weeks.

The method of performing the differential cell count was as follows:-

Blood films, which were thin, and evenly spread, were made on microscopic slides, and stained with Leishman's stain. The concentrated stain was allowed to act for two minutes and then it was diluted with an equal quantity of water, and allowed to act for a further ten minutes. At the end of this time, the stain was gently washed off, and the slide allowed to dry. The

count/

count was performed under the oil immersion lens and the slide moved in all directions to obtain as true an average distribution as possible. The number of cells counted in each case was 300.

It is known that in disease the cells undergo constant alteration. In some diseases they are either increased or diminished, and in others they may vary during the course of the illness. Variations in specific cells are also observed, this being especially so with the neutrophil polymorph and lymphocytes.

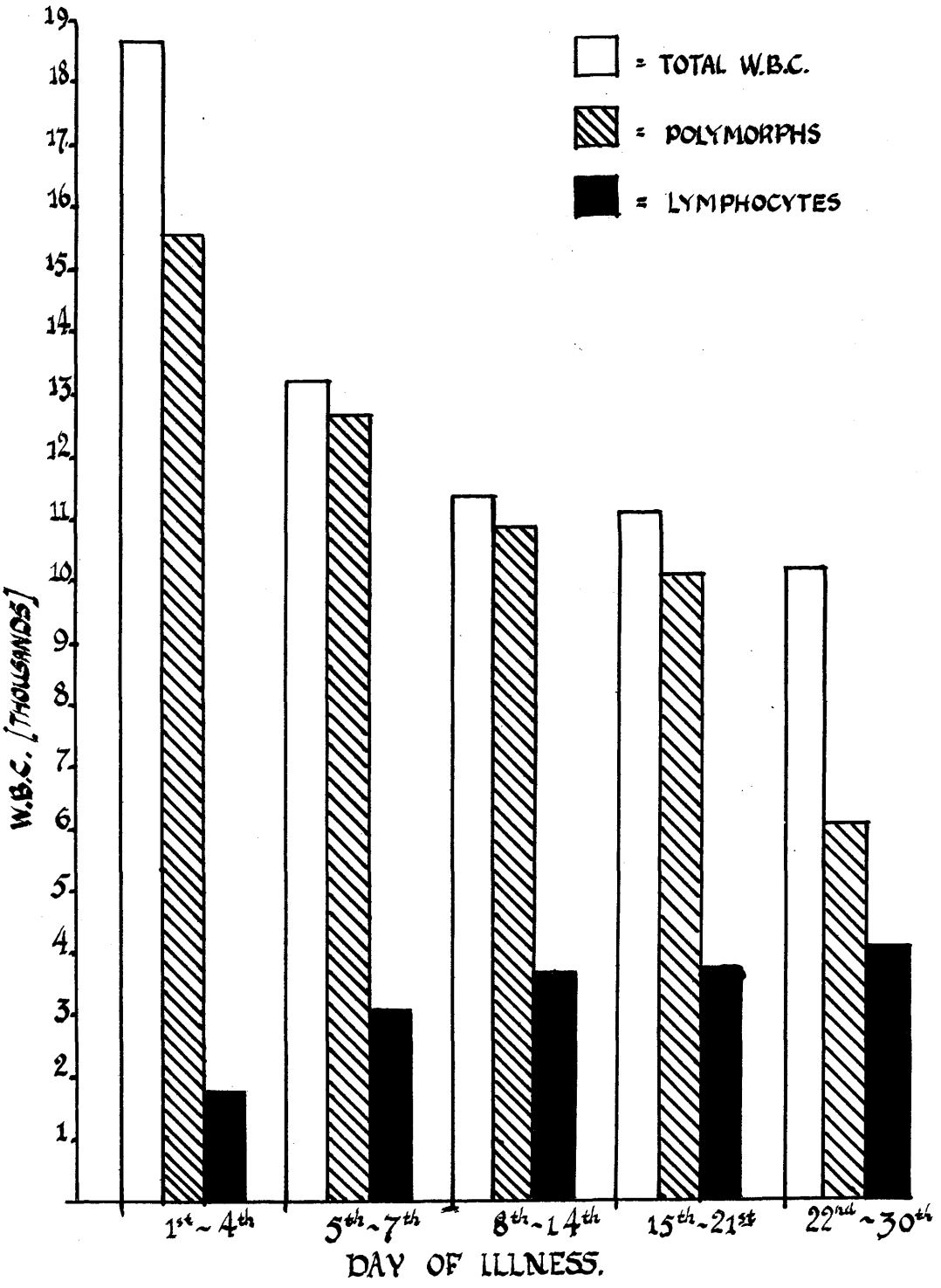
As all the patients were children it was important that controls should be available for comparison, for, as is well known, the white blood cell count is variable in childhood, slight stimuli or change of environment producing disproportionately large/

Fig 1.

Meningococcal Meningitis.

White Blood Cell Counts

[Mean of 77 cases.]



large alterations in the number of circulating leucocytes.

Unfortunately this hospital provided no opportunity for a study of normal children. However, many studies of this kind are to be found in the literature and they almost agree in detail as to the nature and extent of this normal variation, hence the usually stated figures have been used for comparison.

Although the cases were investigated in two groups, those treated with penicillin alone, and those treated with sulphonamide and penicillin, it was found that the difference between the two were so slight that they could be considered as a whole, but should any extensive variation be noticed attention would be drawn to it. The total number of cases in both groups was 100 but only the blood findings in 77 are recorded, the remaining 23 terminated fatally, and the blood readings are necessarily incomplete.

TOTAL LEUCOCYTE COUNT.

During the early acute stage of the illness the total leucocyte count was increased, but as convalescence progressed it steadily dropped to normal, this point being reached from the 8th to 14th day of illness (See Fig. 1). The return to normal was more rapid in the penicillin and sulphonamide group than that treated by penicillin alone. This is understandable in view of the findings with regard to the rate of resolution of the disease in the two treatment groups.

As regards the 23 cases which terminated fatally it was found/

Fig VI.

Meningococcal Meningitis.
Frequency Distribution of Eosinophil Cells.
[77 Cases.]

No of Cells Per C.mm.	Day of Illness.				
	1st~4th	5th~7th	8th~14th	15th~21st	22nd~30th
100	~	~	6	8	~
150	~	~	2	5	~
200	~	~	4	3	4
250	~	~	21	10	1
300	~	~	25	28	7
350	~	~	~	12	15
400	~	~	~	4	50
450	~	~	~	7	~
Total	~	~	58	77	77

Fig III

Meningococcal Meningitis
Frequency Distribution of Monocytes.
[77 Cases.].

No of Cells Per c.mm.	Day of Illness.				
	1st-4th	5th-7th	8th-14th	15th-21st	22nd-30th
150	2	~	~	~	~
200	1	~	~	~	~
250	1	~	~	~	~
300	~	~	~	~	3
350	1	~	2	4	5
400	3	~	1	3	13
450	2	~	1	16	18
500	6	14	4	9	38
550	4	3	~	45	~
600	8	5	23	~	~
650	4	55	37	~	~
700	19	~	9	~	~
750	22	~	~	~	~
800	4	~	~	~	~
Total.	77	77	77	77	77

found that the total cell count had dropped rapidly before death to figures between 3,000 to 7,000 cells per c.m.m.

NEUTROPHIL POLYMORPHS AND LYMPHOCYTES.

A study of the neutrophil polymorph and lymphocytes showed that the former were greatly increased during the early acute stages of the illness and then gradually decreased in number until by the 3rd week the count had returned to normal. The lymphocytes were markedly decreased during the early stages of the illness and gradually increased during convalescence, normal counts being found between the 2nd and 3rd week of illness. (See Fig. 1).

EOSINOPHIL POLYMORYHS.

For the first five days of the disease it was noted that the eosinophils were absent but they began to appear in a proportion of cases about the 6th or 8th days gradually increasing in number until they were present without exception in normal amounts by the 8th and 14th day. (See Fig. 11). In the 23 cases which died they failed to appear.

MONOCYTES.

In studying the monocytes it was observed that they were increased in number at the outset of the disease, and decreased in convalescence, returning to normal about the third week (See Fig. 111). In the cases which terminated fatally, there was no specific alteration in the number of monocytes in the blood.

CONCLUSIONS.

In meningococcal meningitis the eosinophil polymorphs were either absent or diminished during the early acute stages of the disease, and their return to the blood was indicative of returning health, while their disappearance and continued absence was associated with the persistence of infection and presumes a fatal termination. The neutrophil polymorphs were found to be increased during the early acute stages and the lymphocytes were diminished. During convalescence the neutrophils returned to normal, and the lymphocytes increased, returning to normal between 2nd and 3rd week.

CHAPTER VIII.

THE INVESTIGATION OF THE CASES WHICH TERMINATED FATALLY.

In this chapter brief summaries of the histories of all the cases which terminated fatally have been made.

The 16 deaths which occurred in Group A will be considered first. Table No. 30 shows the distribution of the cases terminating fatally in Group A with regard to age, duration of illness before admission, the presence or absence of convulsions, or of coma on admission, the duration of stay in hospital, and the development of sequelae or complications such as hydrocephalus, or gastro-enteritis.

TABLE NO. 30.

DETAILS OF CASES WHICH TERMINATED FATALLY IN GROUP A.

Case.	Age.	Days Ill Before Admission.	Convul-sions.	Coma.	Gastro Enteritis.	Hydro cephalus.	Duration in Hospital.
(1)E.B.	6/52	5	+	+	-	+	8 Days.
(2)DMc	9/52	3	+	-	-	-	2 "
(3)M.G.	11/52	6	+	-	-	+	19 "
(4)B.K.	6/12	3	-	-	2nd Day	-	11 "
(5)D.G.	6/12	2	+	+	"	-	16½ hours.
(6)J.Mc	6/12	1	-	-	7th Day	-	19 Days.
(7)DMc	7/12	1	+	-	8th "	-	11 "
(8)W.Y.	7/12	1	-	+	-	-	1 Day.
(9)D.H.	8/12	2	+	-	-	+	12 Days.
(10)LMc	9/12	2	-	-	5th Day	-	5 "
(11)WS	13/12	1	+	+	-	-	13 Hrs.
(12)HH	3	1	+	-	-	-	7 Days.
(13)CMc	3	4	-	+		+	1 Day.
(14)FS	4	3	-	-	-	+	64 Days.
(15)JR	4	2	-	+	-	-	1 Day.
(16)EC	7/12	2	-	+	-	-	1 "

Case No. 1. E.B.

This patient, aged 6 weeks, was admitted in the 5th day of illness, in a comatose state, with a history of diarrhoea and convulsions for the past three days.

On examination the infant was found to be pale and poorly nourished. The anterior fontanelle was bulging. Kernig's sign and nuchal rigidity were present. She could be aroused on stimulation but irritability was marked.

Lumbar puncture revealed a turbid fluid under increased pressure. The total cell count was 1000 plus cells per c.m.m. and the differential cell count was 80 per cent polymorphs. Meningococci were found in direct film and culture. Penicillin, 50,000 units, were administered intrathecally. Twitchings occurred one hour later which were controlled with one drachm of syrup of chloral. There was no improvement over the next 8 days, the pressure of the cerebrospinal fluid fell markedly at subsequent lumbar punctures and the fluid became opalescent. "Block" was suspected on the 4th day in hospital. Intraperitoneal salines were given to combat dehydration.

AUTOPSY.

There was thick pus at the base of the brain with a cone of adhesions round the brain stem. The lateral ventricles were dilated and there was pus formation in the choroid plexuses. There was pus in the aqueduct of Sylvius. The other organs were normal.

This/

This patient was under 2 months of age, an age at which it is rare to have the disease developing. The duration of illness before therapy was instituted was 5 days, and on admission such manifestations of serious prognostic significance as convulsions, and a comatose state were present. Nuchal rigidity and Kernig's sign were elicited, and the fontanelle was bulging throughout the disease. The prognosis in a case of this kind where the disease was well established in a debilitated child before therapy was instituted was bad from the outset.

Case No. 2 D.Mc. Age 9 Weeks.

The patient was severely ill for 3 days before being admitted with bronchitis and diarrhoea.

On examination he was found to be poorly nourished and had a petechial rash and was convulsing. Nuchal rigidity and Kernig's sign were present; there was no evidence of gastro-enteritis or any intrapulmonary disease.

Lumbar puncture revealed a turbid fluid with a total cell count of 1,000 plus cells per c.m.m. and a differential cell count of 90 per cent polymorphs, penicillin, 50,000 units, were given.

There was no improvement in the clinical condition of the child as indicated by clinical and bacteriological findings and he died on his second day in hospital.

AUTOPSY. Not obtained.

The/

The disease occurred in a debilated child with a poor resistance to infection, so that it is doubtful if any form of therapy would have been of avail. The convulsions present on admission were of serious prognostic significance.

Case No. 3. M.G. - Age 11/52.

The patient was admitted in the 6th day of illness, with a history of vomiting, and convulsions.

On examination the fontanelle was bulging, Kernig's sign and nuchal rigidity were slightly positive. The temperature was not elevated.

Lumbar puncture revealed a turbid fluid with meningococci in direct film and culture. At subsequent lumbar punctures the pressure was low, the fluid opalescent having a total cell count on an average of 400 cells per c.m.m. Considering these findings and in conjunction with the clinical condition "Block" was diagnosed. The condition appeared to be slightly improved at first but this was not maintained. The fontanelle was tense and bulging and there was separation of the cranial sutures, the child being in the characteristic adynamic state associated with hydrocephalus. Death occurred on the 19th day in hospital.

AUTOPSY. Permission not obtained.

The/

The prognosis in this case was grave from the outset, although at first it was thought that there was a response to the treatment. However, the development of hydrocephalus showed that the condition had not resolved with the treatment given but had entered upon a chronic stage.

Case No. 4. B.K. Age 6/12.

The patient was admitted in his third day of illness with a history of frequent vomiting. Stiffness of the neck was also noticed.

On examination the patient was found to be fairly well nourished but was slightly dehydrated. Nuchal rigidity and Kernig's sign were present. Irritability was marked.

Lumbar puncture revealed a turbid fluid under increased pressure. The total cell count was 1,000 plus cells per c.m.m. and the differential cell count was 90 per cent polymorphs. Meningococci were found in the culture. Following intrathecal penicillin, convulsions occurred one hour later which were controlled by syrup of chloral. On the 2nd day loose green stools were passed which increased in severity on succeeding days, and dehydration became evident, calling for intraperitoneal salines. Sulphaguanadine, one gramme, followed by 0.5 of a gramme every four hours, was given. Subsequent lumbar puncture showed the cerebrospinal fluid to be clearing up, and by the 9th day, the total cell count was 150 cells per c.m.m. of which 90 per cent were lymphocytes. Death occurred on the 11th day.

AUTOPSY./

AUTOPSY. Permission not obtained.

Unfortunately the relatives could not be persuaded to allow an autopsy to be performed but from the clinical findings, and from the condition of the cerebrospinal fluid, the meningitis had cleared up, and the immediate cause of death was due to gastro-enteritis.

Case No. 5. D.G. Age 6/12.

This patient was admitted in his third day of illness with a history of vomiting and convulsions.

On examination he was found to be in a semi-comatose state, and was having frequent convulsions. He was dehydrated and had a tense bulging fontanelle. Nuchal rigidity was marked and Kernig's sign was present. The pulse was rapid and irregular. The respirations were rapid but there was no evidence of intrapulmonary disease.

Lumbar puncture revealed a turbid fluid. The total cell count was 1,000 plus cells per c.m.m. The differential cell count was 90 per cent polymorphs. Meningococci were found in the direct film and culture. Penicillin, 50,000 units, were given intrathecally, and normal salines were given intraperitoneally. Adrenalin, minims 5, were administered every 4 hours. Death took place 16½ hours later.

This child was in a moribund condition when admitted and lumbar puncture had to be delayed for six hours until the general condition improved. Death took place before any form of therapy/

therapy could have been of avail.

Case No. 6. J.Mc. Age 6/12.

This patient was admitted in his first day of illness with a history of vomiting, and listlessness.

On examination he was found to be well nourished, nuchal rigidity and Kernig's sign were present, but were not marked. The fontanelle was bulging, dehydration was slight, and the reflexes were normal.

Lumbar Puncture revealed a turbid fluid with a total cell count of 1,000 plus cells per c.m.m. comprising 90 per cent polymorphs. Meningococci were present in direct film and culture. Penicillin, 50,000 units, were administered intrathecally. The cell count at the 9th day was 220 cells per c.m.m. The condition had progressed satisfactorily until the 7th day when gastro-enteritis developed. Sulphaguanadine, grm 1 and grm 0.5 ever four hours, was given, and intraperitoneal salines administered, but to no avail. The diarrhoea and dehydration progressed, the fluid remained opalescent, and death took place on the 19th day.

AUTOPSY. Not obtained.

The patient's resistance was overwhelmed by the super-added infection of gastro-enteritis. The indications were that the penicillin had overcome the meningitis and would have effected a cure if it were not for the new infection.

Case No.7. D.Mc. Age 7/12.

This patient was admitted in the first day of illness with/

with a history of frequent vomiting, marked irritability and convulsions. He was a well nourished child, with a marked Kernig's sign, and nuchal rigidity. The pulse was rapid and of poor quality. The respirations were rapid and shallow, pallor was marked.

Lumbar puncture revealed a turbid fluid with a cell count of 1,000 plus cells per c.m.m. which dropped on the 7th day to a count of 150 cells per c.m.m. of which 40 per cent were polymorphs. Muscular twitchings followed the administration of penicillin at the 3rd, 4th and 5th lumbar punctures. These were controlled by syrup of chloral one drachm. Gastro-enteritis developed on the 8th day with frequent loose stools. Sulphaguanadine was given and intraperitoneal salines but this failed to overcome the infection. Death took place on the 11th day of illness.

AUTOPSY. Permission not obtained.

Again in this case, gastro-enteritis developed as a complication, and the progress of the case suggested that the meningitis was resolving under penicillin treatment.

Case No. 8. G.C. Age 7/12.

This patient was admitted in his first day of illness with symptoms of vomiting and irritability.

On examination he was found to be a well nourished child. Irritability was marked, the fontanelle was bulging, and Kernig's sign was present. He was in a comatose state.

Lumbar/

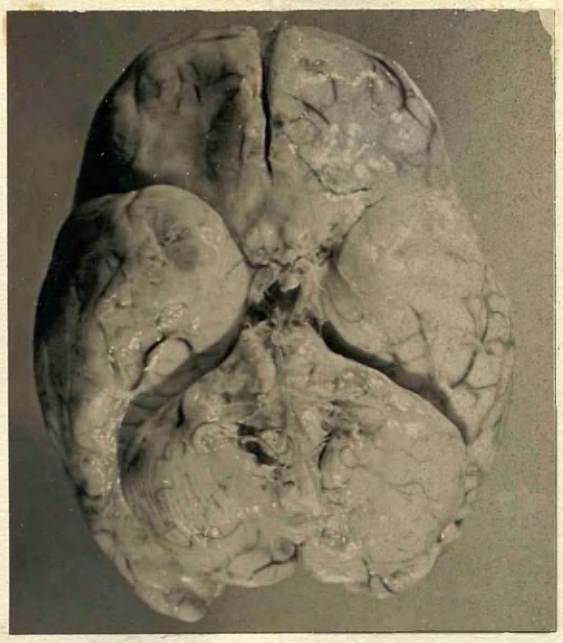


Plate I :- BRAIN; Note pus at base.

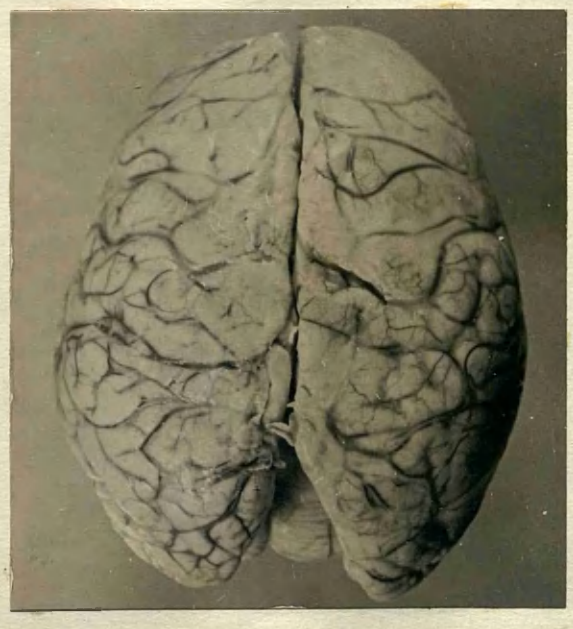


Plate II :- BRAIN; Note pus on ventral aspect.

Lumbar Puncture revealed a turbid fluid with meningococci present in the direct film and culture. The muscular twitchings which followed the intrathecal administration of penicillin were controlled by Syrup of Chloral. Death took place 24 hours later.

AUTOPSY. There was thrombosis of the saggital sinus, with the thrombus extending into the surrounding superficial cerebral vessels. There was marked congestion and oedema of the brain. There was copious pus filling the sulci over the brain surface and at the base. See Plates 1 and 2. All other organs were normal.

This patient had well developed signs of meningitis on his first day of illness, which, together with his particular age group was of grave portent. The reaction following the intrathecal penicillin was a further tax on his strength. A saggital sinus thrombosis was found at autopsy.

Case No. 9 D.H. Age 8/12.

This patient was admitted in his second day of illness with a history of convulsions and vomiting.

On examination he was found to be fairly well nourished and had a positive Kernig's sign and nuchal rigidity. There was slight dehydration and marked pallor.

Lumbar puncture revealed a turbid fluid with a total cell count of 1,000 plus cells per c.m.m. of which 90 per cent were polymorphs. Meningococci were present in the direct film and/

and culture. At first there was a slight improvement in the patient's condition but this was not maintained or borne out by the cerebrospinal fluid findings. Only a small quantity of fluid was obtained on the 9th day a "block" having formed. Death took place on the 12th day in hospital.

AUTOPSY. The brain was oedematous and congested. There were adhesions and pus surrounding the base and spreading up between the temporal and frontal lobes. Both lateral ventricles were distended with cerebrospinal fluid.

The patient was severely ill on admission and was convulsing. His general condition at first appeared to improve but this was not maintained. It is probable that penicillin by itself was not sufficiently effective, and a combination of penicillin and sulphonamide might have been more successful.

Case No. 10. L.Mc. Age 9/12.

This patient was admitted in her 3rd day of illness with a history of irritability and pallor. Head retraction was marked.

On examination she was found to be fairly well nourished, and Kernig's sign was present. Dehydration was slight.

Lumbar Puncture revealed a turbid fluid under pressure. The cell count was 1,000 plus cells per c.m.m. (90 per cent polymorphs) Penicillin, 50,000 units, were injected intrathecally, and intraperitoneal saline was administered. Gastro-enteritis developed on the 5th day, but subsequent lumbar punctures revealed/

revealed no improvement in the cerebrospinal fluid, although the organism could not be isolated. Death took place on the 5th day.

AUTOPSY. Permission was not obtained.

The disease was well established on admission but the clinical condition at the time suggested a fairly hopeful prognosis. The onset of gastro-enteritis on the 5th day overwhelmed the already overtaxed resistance of the child.

Case No. 11. W.S. Age 13/12.

This patient was admitted in his first day of illness in a comatose state with a history of vomiting and convulsions.

On examination nuchal rigidity and Kernig's sign were found to be present. Vomiting was frequent, projectile in type, and he was dehydrated.

Lumbar Puncture revealed a turbid fluid under increased pressure. Meningococci were present in direct film and culture. The total cell count was 1,000 plus cells per c.m.m. of which 90 per cent were polymorphs. Penicillin, 50,000 units, were given intrathecally and muscular twitchings followed its administration. Intraperitoneal saline, eight ounces was also given. The patient died 13 hours after admission.

AUTOPSY. The saggital sinus was thrombosed. The brain presented a cherry pink appearance, particularly round the superficial vessel. Pus extended over the brain surface.

The toxaemia was profound in this case and the appearance of the signs and symptoms of the disease were rapid, the/

the patient being admitted in a comatose state in the first day of illness. Muscular twitchings followed the intrathecal penicillin which was a further tax on the patient's strength. Death took place 13 hours after admission.

Case No. 12. H.H. Age 3 years.

This patient was admitted in his first day of illness with a history of headache, vomiting, convulsions and lassitude.

On examination he was found to be well nourished. There was slight inflammation of the fauces, nuchal rigidity and Kernig's sign were present.

Lumbar puncture revealed a turbid fluid under increased pressure. The total cell count was 1,000 plus cells per c.m.m. with a differential cell count of 90 per cent polymorphs. Penicillin, 50,000 units, were administered intrathecally following each lumbar puncture. There was no improvement in the fluid withdrawn at subsequent punctures.

On the 4th day the patient became very drowsy and was not drinking. Intravenous saline was given, but the condition rapidly deteriorated and death took place on the 7th day in hospital.

Following the administration of the first dose of penicillin there were slight muscular twitchings.

AUTOPSY. There was some pus over the occipital convolutions, and the brain was oedamatous and congested. There was a thrombosis/

thrombosis of the saggital sinus in the posterior 1/2. There was no pus in the ventricles.

This child on admission was severely ill and was having convulsions. The condition at first improved but then relapsed. A saggital sinus thrombosis was found at post mortem. The prognosis from the outset was grave, but it was thought that a greater degree of success should have attended the institution of treatment.

Case No. 13. C.Mc. Age 3.

This patient was admitted to the hospital in his 4th day of illness with a history of headache, shivering, loss of appetite and vomiting.

On examination he was found to be well nourished but was slightly dehydrated and was in a comatose state. Head retraction and Kernig's sign were present.

Lumbar Puncture revealed a turbid fluid with a cell count of 1,000 plus cells per c.m.m. The differential cell count was 90 per cent polymorphs.

Meningococci which were present in the direct film were extracellular in increased numbers. Penicillin, 50,000 units, were administered intrathecally and this was followed by muscular twitchings which were controlled by one drachm of syrup of chloral. The temperature reached 104°F prior to death.

AUTOPSY. There was pus covering the surface and base of the brain and at the base there were also adhesions. There was slight/

slight dilitation of the lateral ventricles which contained pus. Thrombosis of the middle one third of the saggital sinus was present.

At autopsy in this case there was evidence of slight dilitation of the lateral ventricles and in association with the pus and adhesions present suggested that the disease was of longer standing than four days before admission. Muscular twitchings again occurred in this case following the intrathecal penicillin.

Case No. 14. E.S. Age 4 Years.

This patient was admitted in her 3rd day of illness with a history of severe headaches, vomiting, and irritability.

On examination she was found to be fairly well nourished and had definite nuchal rigidity and a positive Kernig's sign. She was severely ill, with a temperature of 103°F.

Lumbar Puncture revealed an opalescent fluid under moderate pressure, with a total cell count of 220 cells per c.m.m. comprising 70 per cent polymorphs. Meningococci were found in culture. The following day her condition had improved, the headaches had disappeared, and the temperature had dropped. On the 3rd day the temperature again became elevated to 101°F and nuchal rigidity and Kernig's sign were well marked.

Lumbar Puncture revealed a very opalescent fluid with a total and differential cell count of 340 cells per c.m.m. and 60 per cent polymorphs respectively.

Penicillin/

Penicillin, 50,000 units, were again administered.

The following day her condition was brighter and the nuchal rigidity and Kernig's sign were less.

A further lumbar puncture at this stage revealed a slightly opalescent fluid under slightly increased pressure with a total and differential cell count of 330 cells per c.m.m. and 60 per cent lymphocytes respectively.

On the 9th day the temperature became elevated with an exacerbation of symptoms - headache, nuchal rigidity, and Kernig's sign were present. The temperature was elevated to 103°F, and lumbar puncture revealed a total and differential cell count of 600 cells per c.m.m. and 70 per cent polymorphs respectively.

Penicillin, 50,000 units, were administered and sulphapyridine two grammes followed by one gramme every four hours, were given.

The temperature dropped to normal in 24 hours and there was a definite improvement. Slight headache remained, but nuchal rigidity and Kernig's sign were less marked. This improvement however was not maintained as the temperature was again elevated and the symptoms and signs became worse.

Lumbar puncture revealed a very opalescent fluid with a total cell count of 440 cells per c.m.m. of which 60 per cent were polymorphs.

The illness from this stage ran a chronic course with evidence/

Plates of two cases showing Hydrocephalus.

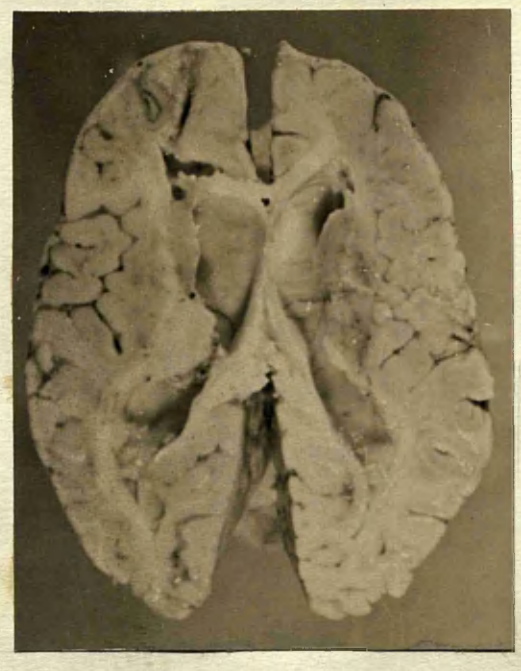


Plate III.

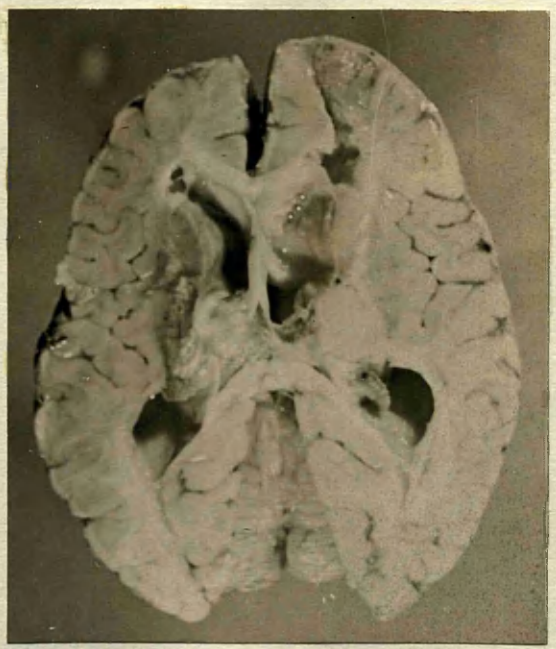


Plate IV.

evidence of hydrocephalus having developed. The cell count ranged between 300 to 800 cells per c.m.m. at subsequent lumbar punctures, until, eventually no fluid could be obtained there being a complete "block". A right internal strabismus developed before death. The patient died on the 64th day in hospital.

AUTOPSY. The brain was oedematous and congested with marked distension of the lateral ventricles. There was a mass of exudate and adhesions at the base. (See Plates 3 and 4).

In this case the condition at first responded well to penicillin and was clearing up but then relapsed. The penicillin was not successful in completely eradicating the infection and when the exacerbation occurred treatment with penicillin and sulphonamide was commenced. The response was at first good but the disease had passed into the chronic stage and hydrocephalus developed. The combined form of therapy might have been more successful if employed from the outset.

Case No. 15. J.R. Age 4 years.

This patient was admitted on his second day of illness with a history of vomiting, severe headache and listlessness.

On examination he was found to be poorly nourished and in a comatose state. He was dehydrated, and had a rapid weak pulse. He had a profuse petechial rash with marked nuchal rigidity and a positive Kernig's sign.

Lumbar Puncture revealed a turbid fluid under markedly increased/

CASE No. 15., J.R.

Thrombosis of right sigmoid sinus

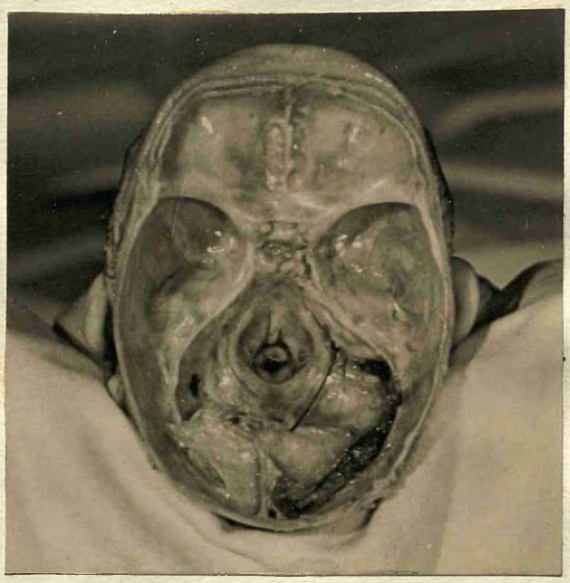


Plate V:- FRONT VIEW.

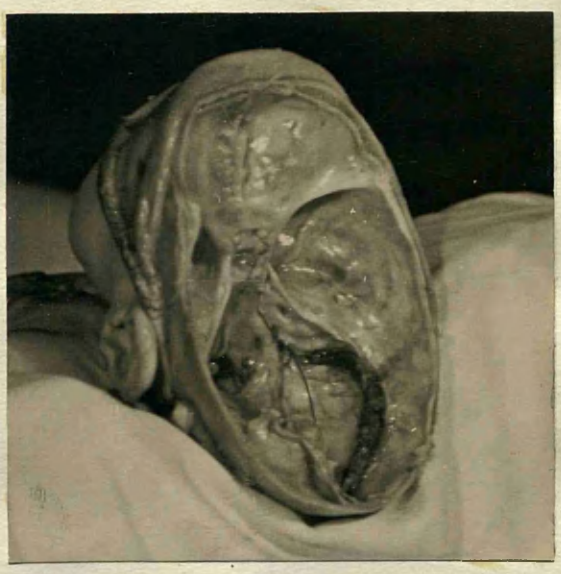


Plate VI:- SIDE VIEW.

increased pressure and a total cell count of 1,000 plus cells per c.m.m. of which 90 per cent were polymorphs.

Penicillin 50,000 units, were administered intrathecally, and intraperitoneal saline was also given. Coramine ½ cc was administered.

The treatment was unavailing for he died 24 hours later.

AUTOPSY. The brain surface was covered with pus particularly at the base and in the ventricles. There was a thrombosis of the saggital and sigmoid sinuses. (See Plates V and VI).

This was a poorly nourished child in extremis when admitted. His resistance to infection was slight and the progress to a fatal termination was rapid.

Case No. 16. E.C. Age 7/12.

This patient was admitted to hospital in her second day of illness with a history of vomiting and diarrhoea. She was in a comatose condition on admission, and there was a pronounced petechial eruption on her trunk and limbs. Nuchal rigidity and Kernig's sign were slightly positive.

Lumbar Puncture revealed a turbid fluid under increased pressure with a total and differential cell count of 1,000 plus cells per c.m.m., and 90 per cent polymorphs respectively. Meningococci were present in the direct film and culture.

Penicillin, 50,000 units, were administered intrathecally and 300,000 units intramuscularly. She was given coramine ½ cc., and intraperitoneal saline. She died two hours after admission.

AUTOPSY./

AUTOPSY. The brain surface was covered with small flecks of pus whichwere particularly thick at the base. The brain was oedematous and congested. All other organs appeared normal.

The infection in this case was of a particularly virulent type and the child was in extremis on admission and it is doubtful if any form of therapy would have been of value.

GROUP B CASES.

In this group there were 7 cases which terminated fatally. The following Table No. 31 shows their distribution with regard to age, duration of illness before admission, the length of stay in the hospital before death occurred, the presence or absence of convulsions or of coma on admission, and the development of gastro-enteritis or hydrocephalus.

TABLE NO. 31.

DETAILS OF CASES WHICH TERMINATED FATALLY IN GROUP B.

Case.	Age of Patient.	Days Ill Before Admission.	Presence or Absence of Conv.	Presence or Absence of Coma.	Presence or Absence of Gastro-enteritis.	Presence or Absence of Hydro-cephalus.	Duration of stay in Hosp.
J.L.	4/52	2	+	+	-	-	2
B.B.	3/12	1	-	+			2
S.P.	9/12	2	+	-	-	-	1
E.G.	10/12	6	+	+	-	-	7
G.S.	4/12	3	-	+	-	-	4
S.B.	18/12	3	+	-	-	-	1
T.P.L.	6/12	7	+	-	-	-	3

Case No. 1. J.L. Age 4 Weeks.

This patient was admitted in her second day of illness with a history of disinclination to take feeds, diarrhoea vomiting and convulsions. On examination she was found to be fairly/

fairly well nourished and nuchal rigidity and Kernig's sign were present. She was in a comatose state. Lumbar Puncture revealed a turbid fluid under pressure, cell count 1,000 plus cells per c.m.m.. The differential cell count was 90 per cent polymorphs. Meningococci were found in direct film and culture. Intraperitoneal saline, 6 ounces, were given. The following day the condition did not improve, the nuchal rigidity became more pronounced and the coma deepened. Lumbar puncture revealed a still turbid fluid under increased pressure. No meningococci were found either in direct film or culture. She died on her second day in hospital.

This patient was 4 weeks old and severely ill when admitted being dehydrated and in a comatose condition. The attempts to overcome the infection and the dehydration were unavailing, the disease having assumed a fairly virulent form which gave a grave prognosis from the outset. Death took place within 48 hours of admission.

Case No. 2. B.B. Age 3 months.

This patient was admitted in her first day of illness with a history of vomiting and marked irritability. On examination she was found to be dehydrated but was fairly well nourished. Nuchal Rigidity and Kernig's sign were slightly positive. She was in a comatose state.

Lumbar Puncture showed a turbid fluid under increased pressure with a total cell count of 1,000 plus cells per c.m.m. and a differential/

differential cell count of 90 per cent polymorphs. Penicillin, 30,000 units intrathecally, and sulphonamide, one gramme followed by half a gramme four hourly, were given.

Subsequent lumbar puncture revealed a turbid fluid but no organisms were present. The condition did not improve and he died on the 4th day in hospital. The disease progressed with rapidity in this infant and the treatment did not have any apparent influence on its course.

Case No. 3 S.P. 9 months.

This patient was admitted in a comatose state in her 2nd day of illness with a history of frequent vomiting and listlessness. On examination she was found to be fairly well nourished, the fauces were slightly injected. Nuchal rigidity and Kernig's sign were marked. The pulse was of poor quality, irregular and rapid. Her face was flushed.

Lumbar Puncture revealed a turbid fluid under markedly increased pressure with a total and differential cell count of 1,000 plus cells per c.m.m., of which 90 per cent were polymorphs. Meningococci were present in direct film and culture. The patient died 24 hours after admission.

The age of the patient and her collapsed condition justified a grave prognosis from the outset. The therapy employed was unable to exert any beneficial effect as the child was overwhelmed with the infection. She died 24 hours after admission.

No.4. S.B./

No. 4 S.B. Age 18 months.

This patient was admitted on his 2nd day of illness, with a history of vomiting, irritability and of having had convulsions. On examination he was found to be a well nourished child. He had a heavily coated tongue, the throat was healthy. Kernig's sign was present and there was well marked nuchal rigidity.

Lumbar puncture revealed a turbid fluid with a cell count of 1,000 plus cells per c.m.m. of which over 90 per cent were polymorphs.

Penicillin, 30,000 units, were injected intrathecally, and sulphonamide, grammes 1.5. followed by one gramme four hourly, were given.

On the following day the respirations became more rapid and the respiratory murmur harsher with crepitations in both lungs. Pneumonia was diagnosed. He lapsed into coma and died within 24 hours of admission.

AUTOPSY. There was marked congestion and oedema of the brain. The saggital sinus was thrombosed. Pus was present round the larger vessels on the brain surface. There was congestion of the left lung with pleurisy, and there were adhesions at the base.

In this patient the meningitis was complicated by a left sided pneumonia which made the prognosis doubly grave. Death occurred 24 hours after admission.

Case No. 5/

Case No. 5. E.G. 10 months.

This patient was admitted in his 6th day of illness with a history of vomiting and convulsions. He was in a comatose state.

On examination, he was found to be poorly nourished and was slightly dehydrated. The anterior fontanelle was bulging, nuchal rigidity was marked, and Kernig's sign was present. Lumbar puncture revealed a turbid fluid having a cell count of 1,000 plus cells per c.m.m. of which over 80 per cent were polymorphs. Meningococci were present in direct film and culture. Penicillin, 30,000 units, were injected intrathecally, and sulphonamide, an initial dose of one gramme and 0.5 grammes thereafter four hourly, were given.
The convulsions which were present on admission persisted and recurred at frequent intervals, but were eventually controlled with syrup of chloral.

There was no improvement over the following seven days. The nuchal rigidity progressed to head retraction and opisthotonus. The patient died on the seventh day in hospital.
This patient was ten months old, and was admitted in his sixth day of illness in a seriously ill condition with the manifestations of the disease well developed. There was no response to treatment, death occurring on the 7th day in hospital.

Case No. 6. P.L. Age 6 months.

This patient was admitted with a history of having been/

been ill for a considerable time before admission. He was listless, and before admission had started to have convulsions. On examination he was found to be emaciated and had a widespread eczema involving the scalp. Nuchal rigidity and Kernig's sign were marked. He was very irritable and had a petechial rash.

Lumbar puncture revealed a turbid fluid under increased pressure, with a total and differential cell count of 1,000 plus cells per c.m.m. and 90 per cent polymorphs respectively. Meningococci were found to be present in culture.

On the morning of the 3rd day in hospital he was again lumbar punctured but there was no improvement in his condition. There were no organisms found in a film or culture.

This child had a vague history of ill health for some time before admission and this had left him in a very debilitated condition. The resistance of the child as a result of his previous ill health was so low that even although treatment with penicillin and sulphonamide was instituted, the disease progressed and death took place within 2 days of admission to hospital.

Case No. 7. G.S. Age 4 months.

This patient was admitted in a comatose state in his second day of illness with a history of having been fevered, irritable, and vomiting. On examination he was found to be well nourished but dehydrated. He had a bulging fontanelle with/

with well developed nuchal rigidity and a positive Kernig's sign.

Lumbar puncture revealed a turbid fluid with a total and differential cell count of 1,000 plus cells per c.m.m. and 90 per cent polymorphs respectively.

Penicillin, 30,000 units, were given intrathecally, and sulphonamide, one gramme followed by 0.5 gramme four hourly. Intraperitoneal salines were given. There was no improvement in the patients condition over the period of four days in hospital. Lumbar puncture after the third day revealed a turbid fluid but no organisms were found.

On the fourth day the condition deteriorated still more and death ensued.

The disease progressed rapidly in this case and the combined form of therapy instituted did not have much influence on it. The age of the patient, and the degree of dehydration resulting from the frequent vomiting, were factors which were difficult to combat and made the prognosis grave.

DISCUSSION.

All the cases dealt with in this series were of sporadic occurrence but in some patients the disease approached in severity the epidemic form. The majority were under two years of age, an age group in which cerebrospinal fever has always taken a heavy toll of life. The distribution of the severely ill patients in both groups was fairly even, although there tended to be a few who exhibited features of graver prognostic significance in the penicillin treated group.

The fatality rate in the penicillin treated cases was 32 per cent as compared with 18 per cent in those who were given penicillin and sulphonamide. These fatality rates are high and do no compare favourably with those of other workers using the sulphonamides, even when one takes into consideration the fact that the majority of patients were under two years. Banks (1939) for example, treated a series of 72 cases with sulphonamides, of which 49 were aged 5 years or under and his fatality rate was 1.4 per cent, there were no deaths in the children under 5 years of age. It is true that the cases treated in his series may have differed in many respects from those dealt with in this work and no true comparison can be made, yet the difference in the fatality rates is remarkable. Similarly the Scientific Advisory Committee to the Department of Health for Scotland reviewed in 1944 2,223 cases of cerebrospinal fever,/

fever, some of which occurred during an epidemic period when the incidence of severe and fulminating forms were high, and their fatality rate in 280 cases of one year of age and under treated with sulphonamides was 18.7 per cent. In the penicillin, and penicillin and sulphonamide treated groups in this study, the fatality rates for this age group were higher by 33.3 per cent and 8.5 per cent respectively. Banks, in his series of cases further observed that the temperature generally returned to normal and the acute symptoms had cleared up in from two to six days; the cerebrospinal fluid was sterile within twenty four hours and the cell counts fell rapidly to 500 c.m.m. or less by the third or fourth day of treatment. At the end of ten to fourteen days the cerebrospinal fluid was quite normal.

In the cases treated by penicillin alone, and with penicillin and sulphonamides, the acute stage of the illness was more prolonged than this. The primary pyrexia in several of the cases in Groups A and B lasted until the tenth and seventh day of illness respectively. The cerebrospinal fluid in the penicillin treated cases had cell counts of from 150 to 450 cells per c.m.m. in the greater number of cases until the fifteenth day and in those treated with penicillin and sulphonamide until the eleventh day.

Although the cerebrospinal fluid had a high cellular content for several days, yet forty eight hours after the intrathecal/

intrathecal injection of penicillin, the meningococcus could not be found in either film or culture in any of the cases in either Group A or B. It is surprising therefore that the disease did not resolve more rapidly, particularly in the cases which were treated with an adequate dosage of sulphonamides in addition to penicillin. Something was responsible for prolonging the illness, and suspicion fell on the penicillin, for it was shown by other workers that intrathecal penicillin tended to produce what amounted to an aseptic meningitis. Rammelkamp and Keefer (1943) have shown that intrathecal penicillin causes a pleocytosis of the cerebrospinal fluid. Rosenberg and Arling (1944) noted that cases of meningococcal meningitis which were treated with large doses of penicillin had more severe and persistent headaches, the fever was more prolonged, and the signs of meningitis subsided more slowly. These findings lent confirmation to the suspicion which was aroused that penicillin in large doses did tend to prolong the illness as a result of its irritant effect on the central nervous system. Those patients who received the large intrathecal dose of 50,000 units developed more severe reactions in the form of lumbo-sacral pain or convulsions. The children who developed these reactions were all four years of age or under. Convulsions occurred in twenty cases and 77.2 per cent of the patients affected were two years of age or under. The younger the patient, the higher was the incidence of the reactions./

reactions. In seventeen of the patients evidence of toxicity to the intrathecal penicillin followed the first or second dose, which suggests that during the early acute stage of the illness the central nervous system was more sensitive to the impurities of the drug. Lumbo-sacral pain was complained of in seven cases all of which were aged from thirteen months to four years. It is possible that this reaction was experienced by younger children but no definite evidence could be obtained as they were incapable of describing their symptoms. The pain was at its maximum intensity immediately after the injection and then gradually passed off in about five minutes, A possible explanation for this reaction is that the concentrated solution of penicillin was more irritant to the cauda equina and then as it diffused and was diluted in the cerebrospinal fluid, the symptoms subsided. However this concentration was sufficient to cause the convulsions which occurred later,

The impurities present in the salts are mainly pyrogenes and although the products of each manufacturer conform to the required standard of purity (300 units of penicillin per milligramme) their toxicity varies. The salts used in the experiment varied in potency from 300 to 500 units per milligramme, but the amount of impurities present when a large dose was given was sufficient to cause toxic reactions.

Although in this study the penicillin was administered in a large dose yet it was insufficient to provide a bacteriostatic/

bacteriostatic action for the whole interval of forty-eight hours between the intrathecal injections. The bacteriostatic titre estimations showed that it was not until the seventh day that a therapeutic concentration of penicillin was obtained in the cerebrospinal fluid forty-eight hours after its injection.

The cases in Group B received a dose of 30,000 units which being smaller was more rapidly excreted so that even when convalescence was reached, the number showing a rise in titre was few. The concentration of penicillin in the cerebrospinal fluid was at its maximum immediately after the injection and then steadily fell as it was excreted. The excretion was rapid during the acute stage of the illness when the blood-brain "barrier" was most impaired but it steadily fell as the efficiency of the "barrier" improved with the recovery of the patient. The bacteriostatic titre estimations show that the penicillin was completely excreted before the next injection during the first few days of the illness. Thus there was a period during which the infection could have reasserted itself, and it is highly probable that this was a factor which prolonged the disease in some of the cases treated by penicillin, and predisposed to sequelae such as hydrocephalus.

In Group B cases a smaller dose of penicillin was given but the sulphonamides administered at regular intervals exercised a constant bacteriostatic action on the infection and recovery was thus more rapid. To maintain an adequate

penicillin/

penicillin level over the first few days of illness the drug, if administered intrathecally, would require to be injected daily in a smaller dose. Frequent intrathecal injections, however, no matter the effectiveness of the aseptic technique employed, carry a definite risk of introducing a secondary infection. In addition, the discomfort and strain on a severely ill patient would be hardly justifiable.

The treatment of meningococcal meningitis in children below the age of five years with intrathecal penicillin was not a success, and its routine employment is not justified, particularly when the sulphonamides give such excellent results. However, if a patient does not respond adequately to the sulphonamides, intrathecal penicillin in smaller doses and at more frequent intervals could be resorted to, provided the infecting organism is penicillin sensitive. Cairns (1946), for example, reports good results from the treatment of pneumococcal meningitis with sulphadiazine and intrathecal penicillin.

SUMMARY.

Fifty cases of meningococcal meningitis were treated with intrathecal penicillin alone, and a further fifty cases with sulphonamide and intrathecal penicillin.

The patients treated entirely with intrathecal penicillin were given a dose of 50,000 units every forty eight hours. The cases which were treated with sulphonamides in addition to the penicillin received a smaller intrathecal dose of 30,000 units.

Blood cultures were taken from 75 patients on admission and all were negative.

The penicillin bacteriostatic titre of the cerebro-spinal fluid was estimated at forty eight hourly intervals after its intrathecal injection, and it was found that its excretion was rapid during the acute stage of the illness.

The quantitative and qualitative changes in the polymorphonuclear leucocytes in the blood of patients suffering from cerebro-spinal fever were investigated. The eosinophil polymorphs were found to be absent or diminished during the early acute stage of the illness and their return to the blood was of favourable prognostic significance.

The two groups of cases were compared and it was found that there were a slightly greater number of severely ill patients among those treated entirely with intrathecal penicillin.

The results obtained from the treatment of the cases with intrathecal penicillin alone were disappointing. The fatality rate was 32 per cent, and the incidence of hydrocephalus and/

and gastro-enteritis was also high.

In the cases which received sulphonamide in addition to the intrathecal penicillin the results were better. The fatality rate was lower by 18 per cent, the illness was of shorter duration and not one of the cases developed hydrocephalus.

Intrathecal penicillin, in doses of 50,000 units, produced toxic reaction in 22 cases which varied from lumbo-sacral pain to convulsions.

The disease was, on the whole, more prolonged in all the cases which received intrathecal penicillin, and the results did not compare favourably with those of other workers using the sulphonamides alone.

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